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OPIOID DEPENDENCE TREATMENT WITH BUPRENORPHINE

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Introduction

Prescription opioid abuse and misuse is associated with many adverse sequela (i.e. overdose death and increasing transition to heroin use) and has significant associated societal costs and excess medical costs.

"Addiction is defined as a cluster of behavioral, cognitive and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use, persisting in drug use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, as well as the possibility of the development of tolerance or development of physical dependence. Physical dependence is not the same as addiction. Newer diagnostic terminology uses the term "opioid use disorder," which includes both milder forms of problematic opioid use as well as addiction."[1] "In 2014, an estimated 1.9 million people had an opioid use disorder related to prescription pain relievers and an estimated 586,000 had an opioid use disorder related to heroin use."[2]

The Centers for Disease Control and Prevention (CDC) describes prescription painkiller overdoses as a public health epidemic and states that the number of prescription painkiller overdose deaths is now greater than those of deaths from heroin and cocaine combined.[3] There has been an alarming increase in deaths in Utah related to misuse of prescription drugs. Prescription drug-related deaths now exceed deaths resulting from automobile crashes in the US and in our state, and it is now the number one cause of unintentional death.[4] According to the National Vital Statistics System Mortality File, opioid analgesics were involved in more than 40% of all drug poisoning deaths in 2008; nearly 15,000 deaths.[3] In Utah, drug overdose deaths began to increase substantially in 2001 and the increase has continued through 2007.[5] In 2005, Utah had the highest rates in the nation of reported nonmedical use of pain relievers and increase in prescription opioid-related deaths."[6] "In 2012, an average of 21 Utah residents each month died as a result of prescription painkiller overdoses, according to the Utah Department of Health."[7] The CDC drug overdose state information include Utah as one of the states with the highest drug overdose death rates: 14.9-27.0 per 100,000 people (National Vital Statistics System, 2008).[3] According to the CDC, "states with higher sales per person and more nonmedical use of prescription painkillers tend to have more deaths from drug overdoses."[3] The CDC stated in a recent report that unintentional drug overdose death rates in the United States have increased five-fold since 1990 and has been driven by increased use of opioid analgesics.[6] "The opioid epidemic that is afflicting our nation resulted in nearly 30,000 deaths last year."[8] The CDC report that a big part of the problem is nonmedical use of prescription painkillers. "In 2010, about 12 million Americans (age 12 or older) reported nonmedical use of prescription painkillers in the past year."[3]

Results of a retrospective drug use evaluation (published in 2008) of patients receiving buprenorphine/naloxone in a managed care population indicated that "almost half (47.5%) of patients requiring opioid detoxification did not receive prescription opioids through an outpatient pharmacy during the 6-month period preceding opioid detoxification", suggesting that these patients obtained "opioids illicitly, or used other illicit drugs, such as heroin."[9,10]

Controlled prescription drug (CPD) diversion has an increasing financial impact on the Medicaid program and it is not just the cost of the prescription drugs, but also doctor's visits, emergency department (ED) treatment, rehabilitation centers and other health care needs. According to the National Drug Threat Assessment report, National Survey of Drug Use and Health (NSDUH) data and the Drug Enforcement Agency (DEA), opioid pain relievers are the most commonly diverted CPDs. In 2008, opioid painkillers were associated with approximately 305,885 ED visits (Drug Abuse Warning Network; DAWN).[11] In 2009,

misuse or abuse of prescription painkillers resulted in nearly half a million emergency department visits (CDC).[3]

Groups that are more likely to abuse or overdose on prescription painkillers include men, middle-aged adults, people in rural counties, and Whites (1 in 20) and American Indian or Alaska Natives (1 in 10).[3] In Utah, opioid pain medications have been mostly responsible for the increase in deaths in prescription drugs.[4,12]

Background

The treatment of opioid dependence is essential to improve the overall well-being of the patients and families affected. *"Medication-assisted treatment (MAT) is a comprehensive approach that combines approved medications (currently, methadone, buprenorphine or naltrexone) with counseling and other behavioral therapies to treat patients with opioid use disorder."*[1] This has been *"found to reduce morbidity and mortality, decrease overdose deaths, reduce transmission of infectious disease, increase treatment retention, improve social functioning, and reduce criminal activity."*[13,14] Guidelines and health organizations recommend opioid abuse treatment.[15] "*Expanding the use and availability of MAT options like buprenorphine is an important component of the FDA's opioid action plan and one of three top priorities for the U.S. Department of Health and Human Services' Opioid Initiative aimed at reducing prescription opioid and heroin related overdose, death and dependence."*[1] According to the Winter 2016 Substance Abuse and Mental Health Services Administration (SAMHSA) advisory, *"despite governmental and professional endorsement of MAT, and potential patients' apparent interest in it, there remains a significant gap between the need for and the availability of this treatment."*[13,16,17]

Methadone is an opioid analgesic with unique features, including a slow onset of action and long elimination half-life, which make it an effective treatment option for both detoxification and long-term treatment of opioid dependence. Methadone treatment for opioid dependence may only be performed in a highly structured methadone clinic.[18]

Buprenorphine is a partial opioid agonist (so similar, but weaker effects than those of full opioids such as heroin and methadone) with a long duration of action which also makes it an effective treatment option for both detoxification and long-term treatment of opioid dependence.[18,19] Buprenorphine for the treatment of opioid dependence can be prescribed or dispensed by qualified US physicians (required to acquire and maintain certifications to legally dispense opioid dependency medications) in physician offices, community hospitals, health departments, or correctional facilities (Under the Drug Addiction Treatment act of 2000/DATA 2000; refer to appendix 5 Buprenorphine Waiver Management).[18] Until recently, buprenorphine for the treatment of opioid dependence was only available in the US as an oral pill or film formulation. Agents include buprenorphine sublingual tablet (generic; Subutex; latter was discontinued due to abuse potential), buprenorphine/naloxone sublingual tablet (generic; Zubsolv®), buprenorphine/naloxone buccal film (Bunavail®), and buprenorphine/naloxone sublingual film (Suboxone®). "Generic formulations of single ingredient buprenorphine tablets have been available in the US since late 2009, and combination tablets since February 2013."[20] In May 2016, the FDA approved the first buprenorphine implant (Probuphine) for the maintenance treatment of opioid dependence.[1] Buprenorphine implant (Probuphine) provides a constant low-level dose of buprenorphine for six months and is indicated in "patients who are already stable on low-to-moderate doses of other forms of buprenorphine, as part of a complete treatment program" (that includes counseling and psychosocial support).[1]

Naltrexone and naloxone are opioid antagonists. Naltrexone is used in the treatment of opioid dependence only after the patient has been opioid-free for at least 5-10 days to avoid withdrawal symptoms. Naloxone is used as an antidote in opioid overdose. When added to buprenorphine, naloxone is also used to reduce the rate of buprenorphine abuse. The buprenorphine/naloxone combination agents are effective opioid dependence treatment options but are not recommended in the initial detoxification of patients using long-acting opioids, as it may increase risk and severity of withdrawal symptoms.[19] Withdrawal is characterized by a spectrum of symptoms, including rhinorrhea, sweating, restless sleep, weakness, chills, nausea and vomiting, muscle aches, involuntary movements, hyperpnea, hyperthermia and hypertension.[19]

The purpose of this review is to ensure appropriate use of buprenorphine containing products in opioid abuse treatment. The aim is to facilitate access to buprenorphine treatment whilst preventing potential misuse or abuse without unnecessary hindering of access. It is important to review this topic because widespread buprenorphine availability increases the risk of diversion, misuse/illicit use,[20-23] and adverse consequences such as overdoses/medical emergencies due to ingestion by children[24-28] or in patients at increased risk such as those concurrently taking another opioid, benzodiazepine, alcohol sedatives or certain medications interacting with buprenorphine.[13]

Prior authorization criteria could help to ensure appropriate use, but it is important to ensure that it does not serve as a barrier to treatment.[24] Other potential barriers to opioid dependence treatment access that could be relevant to our population, and that should be considered include requirements for concurrent counseling (aimed at improving adherence, but could deter patients from initiating or continuing treatment if not easily accessible or if patient prefer not to have concurrent counseling services), copayments, "*an insufficient ratio of providers to beneficiaries in many communities,[29] insufficient availability of appointments and treatment slots within clinics,[30] and difficulty for many individuals in rural communities in accessing substance abuse treatment clinics, which are predominantly in urban communities."*[24,29]

Patients can receive buprenorphine in Opioid Treatment Programs (OTPs) similar to methadone and the number of patients that received it via this route increased from 727 (in 2004) to 7,020 (in 2011).[24,31] Patients that received it via non-OTP increased from 1670 (in 2004) to 25,656 (in 2011).[24,31] Substantial numbers of patients that could benefit from substance abuse treatment are Medicaid eligible; and Medicaid is the largest funder of substance abuse treatment.[24,32,33]

"Buprenorphine treatment happens in three phases:

1. ***The Induction Phase*** *("to determine the minimum dose of buprenorphine required to prevent further withdrawal symptoms, reduce cravings, and provide minimal adverse effects"[9]) "is the medically monitored startup of buprenorphine treatment performed in a qualified physician's office or certified OTP using approved buprenorphine products. The medication is administered when a person with an opioid dependency has abstained from using opioids for 12 to 24 hours and is in the early stages of opioid withdrawal. It is important to note that buprenorphine can bring on acute withdrawal for patents who are not in the early stages of withdrawal and who have other opioids in their bloodstream."*[18]
2. ***The Stabilization Phase*** (no more withdrawals symptoms and "typically lasts 1-2 months"[9]) "*begins after a patient has discontinued or greatly reduced their misuse of the problem drug, no longer has cravings, and experiences few, if any, side effects. The buprenorphine dose may need to be adjusted during this phase. Because of the long-acting agent of buprenorphine, once*

patients have been stabilized, they can sometimes switch to alternate-day dosing instead of dosing every day."[18]

3. ***The Maintenance Phase*** (longest phase; "usually lasts at least 6 months and can continue for 2 years or more"[18]) *"occurs when a patient is doing well on a steady dose of buprenorphine. The length of time of the maintenance phase is tailored to each patient and could be indefinite. Once an individual is stabilized, an alternative approach would be to go into a medically supervised withdrawal, which makes the transition from a physically dependent state smoother. People then can engage in further rehabilitation—with or without MAT—to prevent a possible relapse."*[18] Usual dosage ranges and target doses for products can be found in table 3 (appendix 1). The SAMHSA advisory (Winter 2016) states that the optimal maintenance dose of buprenorphine products will vary from patient to patient.[13]

In January 2015, the Utah P&T Committee reviewed the safety and efficacy of the buprenorphine agents and suggested that the use of buprenorphine as a single agent for induction of opioid dependence be reviewed by the DUR Board to determine whether it is necessary to put a prior authorization on buprenorphine single agent claims in terms of duration of use. The thoughts were that buprenorphine as a single agent is used in pain, but it is not recommended for long-term opioid dependence treatment due to its abuse potential; combination products are recommended for long-term opioid dependence treatment. In March 2015, the Utah DUR Board reviewed this topic (buprenorphine single agent) and proposed PA criteria were accepted.[34] Criteria for induction of treatment with buprenorphine single product limit treatment to a maximum of 5 days with a maximum daily dose of 16 mg, and a treatment plan to switch to the combination plan. Separate criteria are required for patients who are pregnant or have a true naloxone allergy. Additional information can be found at https://medicaid.utah.gov/pharmacy/prior-authorization. Prior authorization criteria also exist for Suboxone, Zubsolv, and Bunavail. The opioid agonist antagonist combination agents for substance abuse are included in the Utah Medicaid Preferred Drug List (Currently, Suboxone and Zubsolv are preferred and Bunavail and buprenorphine/naloxone are non-preferred).[35]

Methodology

Relevant information from the Drug Class Review (Opioid Dependence Treatment Agents Buprenorphine & Naloxone report prepared by the University of Utah College of Pharmacy) was incorporated into this report.

A Cochrane Library literature search for systematic reviews was conducted. Medline (PubMed), Up to Date, the Agency for Healthcare Research and Quality (AHRQ), the U.S. Department of Health and Human Services website, the FDA website (including product labeled information), the SAMHSA website, Micromedex and Lexicomp were searched for safety information, systematic reviews, clinical trials, and other guidelines.

Buprenorphine products & Indications

See table 3 (Appendix 1) for a summary of the available buprenorphine-containing agents indicated in the treatment of opioid dependence.

Labelled indications for the different buprenorphine formulations are as follows[36]:

A. <u>Opioid dependence</u>

- **Sublingual tablet (buprenorphine generic; buprenorphine/naloxone generic and Zubsolv®)**
- **Sublingual film (buprenorphine/naloxone: Suboxone)**
- **Buccal film (buprenorphine/naloxone: Bunavail)**
- **Subdermal implant (Probuphine):** "Maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low to moderate doses (≤8 mg/day) of a transmucosal buprenorphine-containing product for 3 months or longer with no need for supplemental dosing or adjustments."[37]

Probuphine implant "consists of four, one-inch-long rods that are implanted under the skin on the inside of the upper arm and provide treatment for six months."[1] "If further treatment is needed, new implants may be inserted in the opposite arm for one additional course of treatment."[1] It has to be implanted and removed surgically by a certified healthcare provider (this required training and certification through the Probuphine Risk Evaluation and Mitigation Strategy program).[1]

In the pipeline

Update received from APhA's Pharmacy Today on 11/16/2016:

"Braeburn Pharmaceuticals and Camurus report that a late-stage trial of weekly and monthly injections of buprenorphine (CAM2038) to treat moderate-to-severe opioid use disorder met FDA and EMA primary endpoints of non-inferiority. The Phase III study involved 428 patients with opioid use disorder. According to the data, CAM2038 achieved the primary objective of statistical non-inferiority compared with daily sublingual buprenorphine/naloxone, the current standard of care, for both FDA and EMA's specified endpoints of responder rate and percent negative urine samples for opioids. Camurus president and CEO Fredrik Tiberg said the findings "provide strong support for our upcoming market authorization applications." The two companies will work with FDA and EMA to start the submission process. FDA has granted fast-track designation for CAM2038 subcutaneous injectable products to treat opioid addiction."[38]

B. <u>Pain management</u>

- **Buccal film (Belbuca): "**Management of pain severe enough to require daily, around-the-clock, long-term, opioid treatment and for which alternative treatment options are inadequate."[39]
- **Transdermal patch (Butrans): "**Management of pain severe enough to require around-the-clock, long-term, opioid treatment and for which alternative treatment options (eg, nonopioid analgesics or immediate-release opioids) are inadequate."[37]
- **Injection (Buprenex or generic):** Management of moderate to severe pain"[37]

Opioid dependence treatment

1) Induction

It is important to note which agents are recommended during induction vs. maintenance treatment. The most appropriate agent (single buprenorphine or combination buprenorphine/naloxone) would depend on the type of opioid dependence:

(a) **Short-acting opioid dependence (or heroin)**

"Initiate treatment with sublingual buprenorphine/naloxone or buprenorphine monotherapy during the induction period for short-acting opioids or heroin; initiate treatment when signs of moderate opioid withdrawal appear and not less than 6 hours after last opioid use. Titrate to adequate maintenance dose as rapidly as possible based on control of acute withdrawal symptoms."[37]

"The combination product, buprenorphine and naloxone, is preferred therapy over buprenorphine monotherapy for induction treatment (and stabilization/maintenance treatment) for short-acting opioid dependence (US Department of Health and Human Services 2005)."[37]

(b) **Long-acting opioids or methadone dependence**

"Buprenorphine/naloxone is not recommended for use during the induction period for long-acting opioids or methadone; initial treatment should begin using buprenorphine monotherapy under supervision. Patients should be switched to the combination product for maintenance and unsupervised therapy."[37]

2) Maintenance

The combination product (buprenorphine and naloxone) is recommended for maintenance and unsupervised therapy.[37]

Inappropriate use

- **Off-label use of buprenorphine containing products indicated in the treatment of opioid dependence, as an analgesic**

  Buprenorphine agents indicated in the treatment of opioid dependence are not indicated for use in pain and such use would be off-label. Off-label use as an analgesic is not appropriate and "There have been reported deaths of opioid naïve individuals who receive a 2 mg sublingual dose of buprenorphine."[40]
- "Probuphine is not appropriate for new entrants to treatment and patients who have not achieved and sustained prolonged clinical stability, while being maintained on buprenorphine 8 mg or less of Subutex or Suboxone sublingual tablet or generic equivalent."[41]
- "Probuphine implants should not be used for additional treatment cycles after one insertion in each upper arm."[41]

Clinical Guidelines

(A) Specific guidance with regards to the use of buprenorphine single agent:

Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction CSAT, 2005[42]
"The combination product, buprenorphine and naloxone, is preferred therapy over buprenorphine monotherapy for induction treatment (and stabilization/maintenance treatment) for short-acting opioid dependence."[36]

(B) Guidance with regards to treatment options for the treatment of opioid dependence

According to the guidelines, pharmacologic treatment options for the treatment of opioid dependence include agonist therapy with methadone, partial agonist therapy with buprenorphine or antagonist therapy with naltrexone.[43] Methadone is the most studied and frequently used agent for opioid dependence; however, methadone therapy is associated with unpredictable dosing patterns and increased risk of cardiac arrhythmias. L-α-acetylmethadol (LAAM) is an opioid analgesic structurally similar to methadone which was withdrawn from the US market due to an increased risk of cardiac arrhythmias.[19] The American Pain Society and the College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society, recently published guidelines for the safer use of methadone. When used for opioid dependence, methadone is only available through specially licensed opioid treatment programs and should be used under the close supervision of an experienced provider.[44]

According to guideline recommendations, the goals of opioid dependence treatment are to "achieve a stable maintenance dose" and to "facilitate patient engagement in a comprehensive program." The selection of an opioid dependence treatment agent should be guided by the individual patient's disease history and personal preference in combination with the provider's assessment of the immediate and chronic effects of therapy and overall health status of the patient.[43,44] In general, methadone and buprenorphine/naloxone are recommended as first-line opioid agonist treatment agents. Guidelines do not recommend one buprenorphine/naloxone combination agent over another. In addition, guidelines do not recommend a specific length of treatment for the opioid agonist agents.

Table 1. Guideline Overview

Guideline	Recommendations
CDC Guideline for Prescribing Opioids for Chronic Pain (2016)[45]	"Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder."[45]
American Society of Addiction Medicine (ASAM), "National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use" (2015)[15,46]	⇨ "Clinicians should consider the patient's preferences, past treatment history, and treatment setting when deciding between the use of methadone, buprenorphine, and naltrexone in the treatment of addiction involving opioid use." ⇨ "The venue in which treatment is provided is as important as the specific medication selected. ○ Opioid Treatment Programs offer daily supervised dosing of methadone, and increasingly of buprenorphine. ○ Naltrexone can be prescribed in any setting by any clinician with the authority to prescribe any medication. ○ In accordance with federal law (21 CFR §1306.07), Office-Based Opioid Treatment (OBOT), which provides medication on a prescribed weekly or monthly basis, is limited to buprenorphine. ○ Clinicians should consider a patient's psychosocial situation, co-occurring disorders, and risk of diversion when determining whether Opioid Treatment Programs (OTP) or OBOT is most appropriate." ⇨ "Methadone is recommended for patients who may benefit from daily dosing and supervision in an OTP, or for patients for whom buprenorphine for the treatment of OUD has been used unsuccessfully in an OTP or OBOT setting." ⇨ "Oral naltrexone for the treatment of OUD is often adversely affected by poor medication adherence. ○ Clinicians should reserve its use for patients who would be able to comply with special techniques to enhance their adherence; e.g. observed dosing. Extended-release injectable naltrexone reduces, but does not eliminate, issues with medication adherence." ○ "The prescribing of benzodiazepines or other sedative-hypnotics should be used with extreme caution in patients who are prescribed methadone or buprenorphine for the treatment of OUD." Refer to guideline for additional information regarding buprenorphine and on treating opioid withdrawal (in which buprenorphine could be used; after a sufficient dose to suppress withdrawal symptoms was given, tapering follows which could range from 3-5 days to as long as 30 days or longer). Special Populations (refer to guidelines for additional information) Psychosocial AND methadone or buprenorphine for all (pregnancy only buprenorphine monoproduct) ⇨ *Pregnant women* "Pregnant women who are physically dependent on opioids should receive treatment using methadone or buprenorphine monoproduct rather than withdrawal management or abstinence." "There is insufficient evidence to recommend the combination buprenorphine/naloxone combination." "Treatment with methadone should be initiated as early as possible during pregnancy." Hospitalization may be advisable. "If a women becomes pregnant while she is receiving naltrexone, it is appropriate to discontinue if the patient and doctor agree that the risk of relapse is low." Naloxone is NOT recommended (unless life threatening overdose)

	"Mothers receiving methadone and buprenorphine monoproduct for the treatment of OUDs should be encouraged to breastfeed." "Dose increases as pregnancy advances" ⇨ *Individuals with pain* "Mild: NSAIDs or acetaminophen Moderate: Increase agonist or add opioid Severe: Discontinue buprenorphine; add high potency opioid (fentanyl)." "Discontinue oral naltrexone 72 hours (or 30 days for ER) before surgery." ⇨ *Adolescents* Federal laws and FDA approvals need to be considered for patients under age 18 ⇨ *Co-Occurring Psychiatric Disorders* Manage drug interactions ⇨ *Individuals in the Criminal Justice System* "There is insufficient evidence to recommend any one treatment as superior to another for prisoners or parolees." Only naltrexone XR is recommended (as antagonist) and not oral naltrexone. "Pharmacotherapy should be initiated a minimum of 30 days prior to release from prison." **From FAQs on ASAM website:** Is there a limit on the number of patients a practitioner may treat with buprenorphine at any one time? "Yes. DATA 2000, as amended in December 2006, specifies that an individual physician may have a maximum of 30 patients on opioid therapy at any one time for the first year. One year after the date on which a physician submitted the initial notification, the physician may submit a second notification of the need and intent to treat up to 100 patients. To increase your patient limit from 30-100, visit http://buprenorphine.samhsa.gov/federal.html. *Frequently Asked Questions about Buprenorphine and DATA 2000 (n.d.). Retrieved May 10, 2011, from http://buprenorphine.samhsa.gov/faq.html#A11."* **NOTE:** However, this has changed. "On July 6, 2016, the Department of Health and Human Services (HHS) announced that it will raise the limit on the number of patients that can receive the addiction medicine buprenorphine to 275 patients per qualified provider.[47] Previously, physicians were limited to treatment of 100 patients."[48]
VA/DoD clinical practice guideline for the management of substance use disorders (2015)[49]	**"Opioid Use Disorder** *Pharmacotherapy* 8. For patients with opioid use disorder, the Work Group recommends offering one of the following medications considering patient preferences • Buprenorphine/naloxone • Methadone in an opioid treatment program (Strong For; Reviewed, New-replaced)

	9. In pregnant women with opioid use disorder for whom buprenorphine is selected, the Work Group suggests offering buprenorphine alone (i.e., without naloxone) considering patient preferences. (Weak For; Reviewed, New-added) 10. For patients with opioid use disorder for whom buprenorphine is indicated, the Work Group recommends individualizing choice of appropriate treatment setting (i.e., opioid treatment program or office-based) considering patient preferences. (Strong For; Reviewed, New-replaced) 11. For patients with opioid use disorder for whom opioid agonist treatment is contraindicated, unacceptable, unavailable, or discontinued and who have established abstinence for a sufficient period of time (see narrative in the original guideline document), the Work Group recommends offering • Extended-release injectable naltrexone (Strong For; Reviewed, New-replaced) 12. There is insufficient evidence to recommend for or against oral naltrexone for treatment of opioid use disorder. (N/A; Reviewed, New-replaced) 13. At initiation of office-based buprenorphine, the Work Group recommends addiction-focused medical management (see narrative in the original guideline document) alone or in conjunction with another psychosocial intervention. (Strong For; Reviewed, New-replaced) *Psychosocial Interventions with or without Pharmacotherapy* 14. For patients in office-based buprenorphine treatment, there is insufficient evidence to recommend for or against any specific psychosocial interventions in addition to addiction-focused medical management. Choice of psychosocial intervention should be made considering patient preferences and provider training/competence. (N/A; Reviewed, New-replaced) 15. In opioid treatment program settings, the Work Group suggest offering individual counseling and/or contingency management, considering patient preferences and provider training/competence. (Weak For; Reviewed, New-replaced) 16. For patients with opioid use disorder for whom opioid use disorder pharmacotherapy is contraindicated, unacceptable or unavailable, there is insufficient evidence to recommend for or against any specific psychosocial interventions. (N/A; Reviewed, New-replaced)"[49] **"Opioid Use Disorder Stabilization and Withdrawal** 33. For patients not yet stabilized from opioid use disorder, the Work Group recommends against withdrawal management alone due to high risk of relapse and overdose (see Recommendations 8 and 11 above). (Strong Against; Reviewed, New-replaced) 34. Among patients with opioid use disorder for whom maintenance agonist treatment is contraindicated, unacceptable, or unavailable, the Work Group recommends using a methadone (in Opioid Treatment Program only) or buprenorphine taper for opioid withdrawal management (see Recommendation 11). (Strong For; Reviewed, New-replaced) 35. For patients with opioid use disorder for whom methadone and buprenorphine are contraindicated, unacceptable, or unavailable, the Work Group recommends offering clonidine as a second-line agent for opioid withdrawal management (see Recommendation 11). (Strong For; Reviewed, New-replaced)"[49]
Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug	<u>Methadone therapy should include:</u> • Patient education on methadone safety • Careful dose initiation and titration of methadone

Dependence, in collaboration with the Heart Rhythm Society (2014)[50]	• Close monitoring and follow-up • Electrocardiograph testing • Use of alternative opioids in patients at high risk of cardiovascular complications
National Institute on Drug Abuse: Principles of Drug Addiction Treatment: A Research-Based Guide (Third Edition; 2012)[51]	Pharmacotherapies for opioid addiction: methadone, buprenorphine, buprenorphine/naloxone (and behavioral therapies) No single treatment is appropriate for everyone and depends on the type of drug and characteristics of the patient. "Effective treatment attends to multiple needs of the individual, not just his or her drug abuse. To be effective, treatment must address the individual's drug abuse and any associated medical, psychological, social, vocational, and legal problems. It is also important that treatment be appropriate to the individual's age, gender, ethnicity, and culture." "Remaining in treatment for an adequate period of time is critical." Appropriate duration depends on type and degree of patient's problems and needs; research indicates at least 3 months for most (to significantly reduce or stop drug use); frequently requires multiple treatment episodes (long-term process); relapses can occur (treatment needs to be reinstated or adjusted); programs should include strategies to engage and keep patients in treatment (to prevent leaving treatment too early).
The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of substance use and related disorders. Part 2: Opioid dependence. (2011)[43]	First-line medications: methadone, buprenorphine or buprenorphine/naloxone Adjunctive medications: clonidine, lofexidine Second-line medications: heroin, naltrexone
Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence (2009)[52]	First-line treatment recommendations: Opioid agonist combined with psychosocial assistance Second-line treatment options: naltrexone *may be useful in preventing relapse in patients who have withdrawn from opioids and are highly motivated to abstain from opioid use Opioid agonists include: oral methadone liquid, sublingual buprenorphine *both medications provide good outcomes; methadone may be recommended over buprenorphine, as it is more effective and costs less; buprenorphine may be more appropriate for patients in whom methadone is unwanted, inappropriate or ineffective

American Psychiatric Association Practice Guideline for the Treatment of Patients With Substance Use Disorders, Second Edition (2006)[44]	Acute opioid intoxication or overdose Mild/Moderate: no treatment Severe: naltrexone* *assess for presence of other substances (alcohol, benzodiazepines, other anxiolytic/sedative agents) Acute withdrawal symptoms buprenorphine, methadone, clonidine Maintenance treatment* methadone, buprenorphine, behavioral therapies, counseling * in patients with a prolonged history (>1 year)
Clinical Guidelines for the use of Buprenorphine in the Treatment of Opioid Addiction (CSAT 2005)[42,53] **Quick Guide for Physicians Based on TIP 40 Clinical Guidelines for the use of Buprenorphine treatment in the Treatment of Opioid Addiction[53]**	Can be used for: • Long-term maintenance: "Appropriate dosages of buprenorphine are more effective than low dosages (20–35 mg) of methadone. A buprenorphine dosage of 8–16 mg/day is equivalent to about 60 mg/day of methadone." • Medically supervised withdrawal (MSW): "Buprenorphine has been used with some success to aid in long-period (more than 30 days) withdrawal from opioids, in moderate-period (between 3 and 30 days) withdrawal, and in short-period (3 days or fewer) withdrawal. However, supervised withdrawal usually is less effective than long-term medical maintenance." Refer to guidelines for additional information. **"Conditions and Circumstances That May Preclude a Patient as a Candidate for Office-Based Buprenorphine Treatment** • Co-occurring dependence on high doses of benzodiazepines or other central nervous system depressants (including alcohol) • Significant untreated co-occurring mental disorders • Active or chronic suicidal or homicidal ideation or attempts • Poor response to previous well-conducted attempts at buprenorphine treatment • Significant medical complications." Please refer to guidance for detailed dosing information ⇨ Induction: Day 1 should not exceed 8 mg. Patients who were on LA opioids (e.g. methadone) should be managed by physicians experienced with the procedure. Day 2 switch to buprenorphine/naloxone combination (if day 1 was monotherapy and patient is not pregnant)." ⇨ Stabilization (1-2 months; physicians see patients at least weekly): Adjustment of doses. "Nearly all patient stabilize on daily doses of 16/4-24/6 mg; some may require up to 32/8 mg daily." Once a stable dose has been reached and patient stopped using illicit drugs, biweekly or monthly visits may be appropriate. ⇨ Maintenance (may be indefinitely or relatively short): "Longer maintenance treatment is associated with less illicit drug use and fewer complications." "Long-term medication management. The design of long-term treatment depends on the patient's treatment goals and on objective signs of treatment success. After a patient is stabilized successfully, decisions to decrease or discontinue buprenorphine should be based on the patient's desire and

commitment to become medication free and on the physician's confidence that tapering will be successful. Factors to consider when determining suitability for long-term medication-free status include
- Stable housing and income
- Adequate psychosocial support
- Absence of legal problems."

Patient Management

"Pharmacotherapy is rarely sufficient treatment for substance dependence. Physicians should refer patients for psychosocial services. Substance abuse counseling and participation in a mutual-help group are necessary for most patients. DATA 2000 stipulates that physicians must have the capacity to refer patients for appropriate counseling and other nonpharmacological therapies.

Patients and physicians should agree on treatment goals and devise a treatment plan. The plan should specify conditions that will result in treatment termination and contingencies for treatment failure."

⇨ Monthly toxicology tests (usually urine screening)

SPECIAL POPULATIONS

Co-occurring medical problems: *"Treating opioid addiction in patients with co-occurring medical conditions is likely to result in better outcomes for the co-occurring conditions than would be achieved if the opioid use were not treated."*

Pregnant women and Neonates:

Pregnancy: "Methadone is the standard treatment for pregnant women who are addicted to opioids. Few studies exist on the use of buprenorphine in pregnant women. Buprenorphine is a Category C agent, which means that the benefits of using the drug in pregnant women may be acceptable despite the risk of adverse effects on the fetus."

Continued heroin use is life threatening (risks of infection, overdose, and intrauterine withdrawal). Standard of care in US: Methadone (has been shown to be safe and effective in both pregnant women and neonates). Buprenorphine use in pregnancy evidence (safety & efficacy) is scarce. FDA category C ("animal reproduction studies have shown an adverse effect on the fetus; there are no adequate, well-controlled human studies; the benefits of buprenorphine in pregnant women may be acceptable despite its risks"). Physician to consider whether buprenorphine is appropriate treatment (if patient already receiving) and "document that patient was informed of and understands the risks of treatment with buprenorphine." Neonatal abstinence syndrome has been reported with buprenorphine use during pregnancy; reported to be less intense than with methadone, but no RCTs.

Adolescents and Young Adults: Buprenorphine may be preferred to methadone because of relative ease of withdrawal (physicians should be familiar with State laws regarding parental consent).

Elderly Patients: Limited evidence; caution advised especially during induction (metabolism and absorption differences)

Patients with co-occurring mental disorders: Assess these before or during initiation of buprenorphine treatment; refer patients with polysubstance abuse for treatment of their other addictions.

	Patients with pain: First non-opioid analgesics; if not relieved, SA opioids can be considered & discontinue buprenorphine; follow induction guidelines to restart buprenorphine. **Patients discharged from controlled environments/ involuntary detoxification** (released from prison or return from extended stays in countries where illicit opioids are difficult to obtain): "Patient assessment should determine the diagnosis of opioid dependence or addiction and the risk of the patient's returning to an addiction lifestyle." **Health Care Professionals Who are Addicted to Opioids:** "Buprenorphine may be an appropriate treatment option for healthcare professionals but should be part of a comprehensive, monitored recovery plan."
Substance Abuse Treatment And Family Therapy: A Treatment Improvement Protocol; TIP 39 (2004)[54]	Adjunctive Pharmacotherapy for Substance Use Disorders: • Disulfiram (Antabuse) for alcohol use and naltrexone (Revia) for alcohol and opioid abuse • Methadone, levo-alpha-acetyl-methadol (LAAM), and buprenorphine for opioids, and naltrexone for alcohol and opioids

Buprenorphine substitution therapy in pregnancy

According to UpToDate, programs treating opioid-dependent pregnant women in the United States use either methadone or buprenorphine as first-line therapy.[55] It is also reported that in 2012, the American College of Obstetricians and Gynecologists (ACOG) concluded that the available evidence "supports the use of buprenorphine as a potential first-line medication for pregnant opioid-dependent women who are new to treatment".[55] For pregnant women who are identified as appropriate candidates for opioid substitution therapy, the authors of UpToDate suggests that methadone remains the standard treatment because of the lack of data on pregnancy outcomes after first trimester buprenorphine exposure, and the lack of data on long-term neurodevelopmental outcomes after in utero exposure.[55] It is also reported that "the available evidence supports the use of buprenorphine as an alternative treatment and some organizations are advocating that buprenorphine be used as a potential first-line medication for pregnant opioid-dependent women who are new to treatment."[55] Some evidence exists that indicates potentially less frequent and less severe neonatal withdrawal when buprenorphine is used, and use of buprenorphine as maintenance therapy during pregnancy has increased, but differences in baseline characteristics could have affected results (between women offered methadone vs. buprenorphine).[55] The authors suggest factors to consider including program availability, availability of comprehensive obstetrical and substance abuse care, and patient preference ("*Buprenorphine provided in an office-based setting allows some privacy since patients do not have to attend a clinic daily for methadone treatment. The patient receives a prescription for buprenorphine for up to 30 days at a time, fills the prescription at a pharmacy, and takes the medication as prescribed on her own. However, lack of frequent clinical contact may make office-based treatments less suitable for some opioid-dependent women").*[55]

"Pros and cons of buprenorphine substitution therapy in pregnancy
Pros

- *Lower risk of overdose*
- *Fewer drug interactions*
- *Ability to be treated on an outpatient basis without the need for daily visits to a licensed treatment program*
- *Dosing of buprenorphine is similar to that in nonpregnant women*
- *Evidence suggesting less severe neonatal withdrawal*
- *Insurance in the United States may cover buprenorphine prescribed by a private physician in an office setting, while not covering methadone prescribed at a substance abuse treatment center*
- *Fewer side effects*
- *Low risk of adverse cardiovascular side effects (in contrast, methadone is associated with small increase in risk of arrhythmia)*

Cons

- *Only limited data are available on pregnancy outcomes after first trimester exposure*
- *Lack of long-term neurodevelopmental outcome data*
- *Clinically important patient dropout rate due to dissatisfaction with the drug*
- *More difficult induction protocol with the potential risk of precipitated withdrawal*
- *Increased risk of diversion* (especially the single agent formulation Subutex)*
- *Less stringent structure of some office-based treatment programs*
- *Reports of maternal hepatic dysfunction and elevated transaminases*
- *Effects of buprenorphine are only partially reversible by naloxone*
- *The maximum daily dose of buprenorphine is 32 mg, due to a ceiling effect, which may not be sufficient in all women (usually those requiring more than 140 mg per day of methadone)*
- *More expensive than methadone*
- *Treatment with methadone may result in greater reduction in illicit opioid use*

** The combination of buprenorphine and naloxone (Suboxone) is not used during pregnancy."*[55]

Clinical Efficacy

Buprenorphine provides a partial agonist effect at opioid receptors.[19,44] Similar to methadone, buprenorphine reduces opioid withdrawal and may inhibit the effects of other opioids. Both agents are effective in maintenance treatment of opioid dependence.[12,13,56,57]

Buprenorphine has poor oral bioavailability which is improved when used via the sublingual and buccal routes. Maintenance treatment with buprenorphine should start with a dose matching the patients opioid use patterns (including level of tolerance, type of opioid(s) used, last opioid use). The usual starting dose of buprenorphine is 4 mg/day which is increased over several days to achieve stable effects for a 24 hour period (usual range 8–24 mg/day).[52]

Cochrane Systematic Review(s)

Maintenance treatment

In a recently published Cochrane review, Mattick et al. evaluated buprenorphine maintenance treatment for opioid dependence with placebo and methadone.[12] This review included 31 trials. The table below summarizes the information briefly and additional abstract information is available in appendix 4.

Evidence comparing methadone and buprenorphine at fixed medium or high doses indicates similar rates of efficacy in increasing treatment retention and decreasing overall opioid use.[12] "However, compared to methadone, buprenorphine retains fewer people when doses are flexibly delivered and at low fixed doses."[12] The authors of this Cochrane review states that flexible dose results are more relevant to patients care because fixed doses are rarely used in clinical practice. They therefore conclude that "methadone is superior to buprenorphine in retaining people in treatment, and methadone equally suppresses illicit use.[12]

Effectiveness of buprenorphine vs placebo and methadone in the treatment of opioid dependence[12,13]

Comparator	Retention in treatment	Suppressing illicit drug use	Safety
Placebo	*High quality evidence:* Effective (superior to placebo) at any dose above 2 mg	*Moderate quality evidence:* Effective at doses of 16 mg or greater (measured by urinalysis); lower doses did not suppress illicit opioid use.	Few studies reported adverse events; two studies compared adverse events: no difference between methadone and buprenorphine; possibly more sedation with methadone
Methadone Flexible dose studies	*High quality evidence:* Less effective than methadone (buprenorphine in flexible doses adjusted to participant need).	*Moderate quality evidence:* For those retained in treatment no difference was observed between buprenorphine or methadone (measured by urinalysis)	
Fixed doses Low dose (≤40 mg & 2- 6 mg buprenorphine)	Low dose methadone more likely to retain patients than low dose buprenorphine		
Medium dose (40-85 mg &	No difference	No difference (urinalysis or self-report)	

Comparator	Retention in treatment	Suppressing illicit drug use	Safety
7-15 mg buprenorphine)			
High dose (≥85 mg & ≥16 mg Buprenorphine)	No difference	No difference in suppression of self-reported heroin use	

Pregnant women

Minozzi et al. in a 2013 Cochrane review assessed maintenance agonist treatments for opiate dependent pregnant women and found four trials (271 patients) comparing methadone with buprenorphine (3 trials) and oral slow-release morphine (1 trial), and did not find significant differences.[58] The authors state that attrition bias (unbalanced high drop-out rates) was a major flaw in these studies, and there is still insufficient evidence and a need for additional comparative RCTs of adequate sample size.[58] *"While methadone seems superior in terms of retaining patients in treatment, buprenorphine seems to lead to less severe neonatal abstinence syndrome."*[58]

Adolescents

Minozzi et al. in a 2014 Cochrane review assessed the effectiveness of maintenance treatments for opiate-dependent adolescents, but the review only included 2 trials (189 patients) and the authors stated that it is therefore difficult to draw conclusions.[59] They speculate that a possible reason for the lack of evidence could be the difficulty in conducting trials with young people due to practical and ethical reasons, and highlight the need for RCTs.[59]

Injecting drug users

Gowing et al. in a 2011 Cochrane review that included 38 studies (12,400 participants) assessed the effect of oral substitution treatment for opioid dependent injecting drug users on risk of behaviors and rates of HIV infections, and found that it reduces drug-related behaviors with a high risk of HIV transmission such as illicit opioid use, injecting use, and sharing of injecting equipment, but has less effect on sex related risk behaviors.[60] However, the authors report limitations such as lack of data from RCTs, methodological quality of the studies, and the high risk of bias.

Additional information

Information on reviews regarding oral naltrexone,[61] slow-release morphine,[62] psychosocial interventions,[63] depression during opioid agonist treatment,[64] and management of opioid withdrawal[65] can be found in the abstract summary table in appendix 4.

Other Systematic Review(s)

Other reviews in the Cochrane Library that met the inclusion criteria for the Database of Abstracts of Reviews of Effects (DARE) were reviewed for additional information that has not already been covered by Cochrane reviews.

Neonatal outcomes

Brogly et al. assessed the effect of prenatal buprenorphine versus methadone exposure on neonatal outcomes, and found that buprenorphine could potentially improve neonatal outcomes, but concluded that more evidence is needed because potential bias could have affected results.[66]

Male sexual dysfunction
Yee et al. evaluated the prevalence of sexual dysfunction in males taking methadone compared to buprenorphine, and found that the incidence was higher among methadone users.[67] *"Patients with sexual difficulty while on methadone treatment were advised to switch to buprenorphine."*[67]

Prison settings
Information (reviews) on opioid maintenance treatment in prison settings have also been included in the table in appendix 4.[68-70]

Randomized Controlled Trial(s)

Probuphine
"The safety and efficacy of Probuphine were demonstrated in a randomized clinical trial of adults who met the clinical criteria for opioid dependence and were considered stable after prior buprenorphine treatment. A response to MAT was measured by urine screening and self-reporting of illicit opioid use during the six month treatment period. Sixty-three percent of Probuphine-treated patients had no evidence of illicit opioid use throughout the six months of treatment – similar to the 64 percent of those who responded to sublingual (under the tongue) buprenorphine alone."[1]

Additional evidence/information

Detoxification treatment

This review focuses on maintenance treatment in opioid dependence and not on detoxification, but information on two systematic reviews have been included below for additional background information.

Adolescents
Minozzi et al. (2014 Cochrane review) assessed the effectiveness of detoxification treatments for opiate dependent adolescents, but could not draw any conclusions based on limited evidence (only two trials) and mentioned the same possible reason as in the maintenance review above for the limited availability of evidence in this population.[59,71] Also, neither of these trials included methadone which according to the authors is still the most frequent drug used for withdrawal.[71]

Amato L, et al. (2013 Cochrane review) evaluated the effectiveness of tapered methadone compared with other detoxification treatments and placebo in managing opioid withdrawal and more information can be found in appendix 4.

Technology Assessments identified through the Cochrane Library

In January 2014, the Canadian Agency for Drugs and Technologies in Health (CADTH) Rapid Response Service reviewed the comparative safety of buprenorphine/naloxone (Suboxone) film versus buprenorphine/naloxone tablets for the treatment of prescription opioid addiction in adult patients and identified one RCT comparing buprenorphine/naloxone film and tablets for the management of opioid

dependence.[72] "The authors identified no significant differences between groups with respect to dose effects, adverse events, or treatment outcomes."[72]

In February 2014, CADTH Rapid Response Service reviewed the comparative clinical effectiveness of Suboxone versus methadone for the detoxification of patients addicted to prescription opioids, and reviewed guidelines on the length of detoxification time using Suboxone in patients addicted to prescription opioids.[73] Note that this review focused on patients addicted to prescription opioids. The authors found one RCT which "suggests that Suboxone and methadone were similar with regards to treatment retention and decreasing use of other opioids in patients with nonmalignant chronic pain and an addiction to a prescription opioid"[74], and one guideline (2009; US Department of Veterans Affairs) that "suggests that a daily dose of Suboxone for 1 to 3 days should eliminate signs and symptoms of opioid withdrawal, suppress opioid cravings, and eliminate illicit opioid use in adults."[75] However, the authors state that the results of the study "should be interpreted with caution due to the small sample size, high discontinuation rates, and relative short duration of study."[73] The VA guideline mentioned earlier has since been updated (2015). Buprenorphine/naloxone or methadone is recommended for opioid use disorder (considering patient preferences).[49] In 2013, the CADTH conducted a similar review, but in patients with opioid dependence and found that Suboxone and methadone had similar clinical effects on retention in treatment and heroin use among adult patients with opioid dependence.[73,76]

Tapering

Authors of a recently published small double-blind, placebo controlled RCT (2 hospital-based research clinics) in 53 opioid-dependent adolescents and young adults found that longer (56-day) buprenorphine taper produces better opioid abstinence and retention outcomes than shorter (28-day) buprenorphine taper for opioid-dependent youth.[77]

Duration of use of buprenorphine as single agent

This evidence and information was discussed during the DUR review meeting in March 2015.

No Cochrane reviews or other reviews specifically focusing on this issue were identified.
Lexicomp:
"Manufacturer's labeling:
Induction: Day 1: 8 mg; Day 2 and subsequent induction days: 16 mg; usual induction dosage range: 12 to 16 mg/day (induction **usually accomplished over 3 to 4 days**). Treatment should begin at least 4 hours after last use of heroin or other short-acting opioids, preferably when first signs of withdrawal appear. Titrating dose to clinical effectiveness should be done as rapidly as possible to prevent undue withdrawal symptoms and patient drop-out during the induction period. There is little controlled experience with induction in patients on methadone or other long-acting opioids; consult expert physician experienced with this procedure.
Maintenance: Target dose: 16 mg/day; in some patients 12 mg/day may be effective; patients should be switched to the buprenorphine/naloxone combination product for maintenance and unsupervised therapy"[78]

According to the buprenorphine single agent product labels, buprenorphine plus naloxone replace buprenorphine typically **after 2 days**.[36,40] Also, it could be used as maintenance treatment for opioid dependence in patients who cannot tolerate naloxone ("typical range 4 to 24 mg once daily SUBLINGUALLY; adjust dosage in 2 to 4 mg increments/decrements to level that holds patient in treatment and suppresses opioid withdrawal effects").[36,40]

Micromedex also includes a three day use option based on O'Connor et al.[79] Three methods of opioid detoxification in a primary care setting (A randomized trial):
"Opioid dependence: rapid opioid detoxification (with naltrexone and clonidine), buprenorphine 3 mg SUBLINGUALLY daily for **3 days**"

Safety

Side effects of buprenorphine are similar than those produced by full opioid agonists, but are less intense because it is a partial agonist.[53] In general, the most common adverse events reported with opioid agents include nausea, vomiting, sedation, pruritus and constipation.[80,81] Serious adverse events which are frequently reported with opioid use include: respiratory depression, urinary retention, hypotension and delirium. Clinical trials demonstrate no differences in rates of serious adverse events when morphine and morphine-like agents are dosed with equianalgesic dosing schemes. Buprenorphine, in particular, is associated with limited respiratory depression and a ceiling effect at higher doses unlike fentanyl and many of the other opioid analgesics.[82] There are case reports of overdose fatalities when buprenorphine is used in pediatric patients (discussed below) or when used in combination with benzodiazepines, especially when used parenterally.[54] Continuous infusion of naloxone can be used to reverse respiratory depression in buprenorphine overdose. Differences in potency between the agents, use of multiple physicians and pharmacies, complicated medication regimens and lack of education and communication between providers and patients are risk factors for increased rates of opioid-related serious adverse effects.[83,84]

All buprenorphine products indicated for use in drug dependence are only available through providers who meet special qualifying requirements and have been assigned a unique identification number.[44]

The most commonly abused opioids generally and among health professionals include heroin, oxycodone, morphine, meperidine and fentanyl. Methadone and buprenorphine are associated with abuse as well but at much lower rates than oxycodone or morphine.[19] It has been reported that when injected intravenously, addicts claim buprenorphine effects are similar to equipotent doses of morphine or heroin.[85] Misuse/abuse/inappropriate use is discussed in more detail in the next section.

"Regular adherence to MAT with buprenorphine reduces opioid withdrawal symptoms and the desire to use, without causing the cycle of highs and lows associated with opioid misuse or abuse. At sufficient doses, it also decreases the pleasurable effects of other opioids, making continued opioid abuse less attractive. According to the Substance Abuse and Mental Health Services Administration, patients receiving MAT for their opioid use disorder cut their risk of death from all causes in half."[1]

The buprenorphine-naloxone combination agents are efficacious in reducing the risk of diversion and abuse as naloxone produces an antagonist effect when crushed and used via the nasal or intravenous route. Buprenorphine therapy is generally safe, is not usually associated with respiratory depression and, upon abrupt cessation, is only associated with a mild withdrawal syndrome. The ceiling effect on respiratory depression in children has been questioned though.

Pediatric deaths
Lovegrove et al. found that buprenorphine was one of the two most commonly implicated active ingredients in emergency hospitalizations that occurred in the United States for unsupervised

prescription medication ingestions among children aged <6 years (2007 through 2011; 75.4% involved 1- or 2-year old children): buprenorphine (7.7%) and clonidine (7.4%).[25] *"Accounting for the number of unique patients who received dispensed prescriptions, the hospitalization rate for unsupervised ingestion of buprenorphine products was significantly higher than rates for all other commonly implicated medications and 97-fold higher than the rate for oxycodone products (200.1 vs 2.1 hospitalizations per 100,000 unique patients)."*[25] The general belief that buprenorphine is safer than methadone because of its ceiling effect on respiratory depression is also brought into question (at least in children) due to a report of a small child that died after ingesting a caretaker's buprenorphine naloxone.[26] Results of a retrospective review at a Medical Center in Maine also indicates an increase in accidental and non-accidental ingestion of methadone and buprenorphine by children in proportion to increased clinical use and availability.[27] Results of another retrospective case review of unintentional pediatric buprenorphine exposures that led to admission to the pediatric intensive care unit at a medical center (Northeastern US) also indicate that the increase use of buprenorphine is associated with an increased risk of accidental exposure in children, and that "buprenorphine exposure in children <3 yrs old can cause significant opioid toxidrome."[28]

Cautions reported on package inserts of buprenorphine/naloxone combination agents[81,86]

- Buprenorphine can be abused in a similar manner to other opioids
- Significant respiratory depression and death may occur with buprenorphine therapy, especially when used via the intravenous (IV) route or in combination with benzodiazepines or other CNS depressants, including alcohol.
- Buprenorphine can cause severe, possibly fatal, respiratory depression in children
- Chronic administration of buprenorphine products can result in opioid-type physical dependence; abrupt discontinuation may cause opioid withdrawal syndrome
- Opioid withdrawal syndrome may occur with parenteral misuse of buprenorphine combination agents in individuals physically dependent on full opioid agonists
- Buprenorphine agents should not be used in patients with hepatic insufficiency
- Buprenorphine agents should not be used in patients driving or operating hazardous machinery
- Neonatal withdrawal syndrome may occur following use of buprenorphine by the mother during pregnancy
- Administration of naloxone causes the release of catecholamines, which may precipitate acute withdrawal or unmask pain in those who regularly take opioids
    - buprenorphine/ naloxone is not recommended for use during the induction period for long-acting opioids or methadone; initial treatment should begin using buprenorphine monotherapy
    - buprenorphine/naloxone products may be used during the induction period for short-acting opioids or heroin; initial treatment should be titrated to adequate maintenance dose as rapidly as possible based on control of acute withdrawal symptoms

"The most common side effects from treatment with Probuphine include implant-site pain, itching, and redness, as well as headache, depression, constipation, nausea, vomiting, back pain, toothache and oropharyngeal pain."[1]

SAMHSA Advisory (Winter 2016) advise overdose prevention education and a prescription for naloxone (in case of overdose) to be considered *"for all patients considering or receiving buprenorphine; these should be provided again prior to discontinuation of MAT."*[13]

"There are relatively few data comparing methadone and buprenorphine outside of specialized opiate treatment centers, and the implications of unstructured medication-assisted treatment of opioid dependence for prevention of treatment-related adverse effects are unknown."[56]

Misuse or abuse/inappropriate use of buprenorphine

"In the final quarter of 2012, approximately 750,000 patients filled prescriptions for buprenorphine in the US (IMS Health Solutions, unpublished data)."[20]

"Buprenorphine abuse is common worldwide" and in the US, data indicates that "buprenorphine sublingual formulations are diverted and utilized outside of an established physician–patient relationship, both for self-medication of withdrawal symptoms and to produce euphoria."[20,23,87,88] Authors of other recently published studies also found motivations for non-prescribed buprenorphine to be for decreasing withdrawal symptoms ("as a means of supporting ongoing illicit drug use"[89]) or to self-initiate detoxification or treatment of opioid dependence, and only a few self-reports of study participants that it is for the euphoric effect[89] "Both buprenorphine and buprenorphine/naloxone may be diverted and misused (e.g., intravenously injected, intranasally administered), particularly buprenorphine."[90] Serious adverse events can occur when injected illicitly e.g. infections or death due to overdose especially when coadministered with benzodiazepines or sedative hypnotics.[90]

In 2011, Yokell et al. reviewed the diversion, misuse, and illicit use of buprenorphine and buprenorphine/naloxone, and suggest that "efforts to control diversion should be considered in concert with efforts to increase access to buprenorphine treatment for individuals with opioid dependence."[87]

Cicero et al. examined the motivations for misusing buprenorphine and the factors that might be responsible for the rapid increase in buprenorphine use.[21] The authors found that it is primarily due to the fact that buprenorphine "serves a variety of functions for the opioid-abusing population: to get high, manage withdrawal sickness, as a substitute for more preferred drugs, to treat pain, manage psychiatric issues and as a self-directed effort to wean themselves off opioids."[21] Use for euphoric reasons appeared to be not the main reason for its misuse, but rather the latter two reasons; using it instead of heroin for example or to self-medicate (withdrawal sickness or to wean off opioids).[21] Results from national surveys that was part of a national postmarketing surveillance program to explore perceptions of patients and physicians regarding buprenorphine/naloxone diversion and abuse showed that "By 2009, 46% of the physicians believed that buprenorphine/naloxone was diverted but 44% believed illegal use was for self-management of withdrawal and 53% believed the source of the medication was substance abuse patients."[22] Abuse and misuse increased between 2005 and 2009 as did the number of tablets sold and the authors conclude that there is a need *"to take active attempts to curb diversion and abuse as well as continuous monitoring and surveillance of all buprenorphine products."*[22] Also, *"Finding a balance of risk/benefit (i.e. diversion and abuse versus expanded treatment) remains a challenge."*[22]

It is important to consider the implications of shifting the balance between access and restriction; "buprenorphine treatment for narcotic addiction has a clinically fluctuating risk/benefit equation that must be continually monitored."[90] Restrictions should be aimed at reducing use for euphoric reasons and should channel use for therapeutic reasons to ensure patients have access to treatment for opioid dependence and if used outside of formal treatment programs to "engage individuals who are currently self-treating opioid dependence with diverted buprenorphine in formal treatment programs with proper medical and psychosocial support."[87] Access to buprenorphine help "individuals regain stability in their

lives and avert negative health consequences associated with opioid abuse and injection."[87] We however have to consider the route of access i.e. a legitimate prescription or diverted buprenorphine (being sold on the street, or access via a family member/friend, etc.), and identify ways in which to ensure treatment access for opioid dependence whilst at the same time combating the dramatic rise of buprenorphine misuse.

Lavonas et al. compared rates of abuse and diversion of three sublingual buprenorphine formulations (single ingredient tablets; naloxone combination tablets and film) using data from the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System Poison Center, Drug Diversion, Opioid Treatment (OTP), Survey of Key Informants' Patients (SKIP), and College Survey Programs through December 2012.[20] *"Abuse rates in the OTP, SKIP, and College Survey Programs were greatest for single ingredient tablets, and abuse rates in the Poison Center Program and illicit diversion rates were greatest for the combination tablets. Combination film rates were significantly less than rates for either tablet formulation in all programs. No geographic pattern could be discerned."*[20]

Recognizing potential buprenorphine misuse

Most pharmacists are aware that recurrent early refill requests may indicate misuse or diversion. Gunderson report on the evaluation of laundering conditions (washing machine and washer/dryer) on four buprenorphine products' packaging and degradation of the products (Suboxone and Bunavail film in foil wrappers, Zubsolv tablets in blister pack, Rexam Screw-loc closure pill container for generic product) because of a patient report of damaged medication due to laundering.[91] After finding that the packaging and contents remained intact apart from some minor cosmetic effects, more structured treatment was implemented for the patient and the results were reviewed with the patient, and he disclosed that he fabricated the story to get additional medication.[91] This is one example of a fabricated story to obtain additional medication and it is important to effectively recognize and address this issue in clinical practice.[91]

Does medical management of patients on opioid analgesics change following a diagnosis of substance abuse?

Paulozzi et al. evaluated this using a national longitudinal health claims data from Market Scan commercial claims database (January 2010-June 2011) and found that more could be done to address the problem because prescribing did not change much.[92] The authors suggests actions such as tapering opioid and benzodiazepine prescriptions, maximizing alternative treatments for pain, and greater use of medication assisted treatment such as buprenorphine could help reduce risk in this population.[92]

Adherence to treatment guidelines

Baxter et al. investigated adherence to current buprenorphine treatment guidelines using administrative data for Massachusetts Medicaid and found that *"there is a significant variability in the structure of buprenorphine treatment provided to Massachusetts Medicaid beneficiaries, and that half or less of episodes include physician and behavioral visits at recommended frequencies."*[93] The authors mention the potential for missing or inaccurate data and that more research is needed.[93]

Treatment access / Underserved areas

Some areas of Utah may be underserved and this should be an important consideration when implementing changes that could negatively impact patients in those areas.

Dick et al. analyzed data (2002-11) to identify counties with opioid treatment shortages and results indicated that the increase in waivered physicians has dramatically increased potential access to opioid agonist treatment so that the percentage of the US population residing in opioid treatment shortage counties declined from 48.6 percent in 2002 to 10.4 percent in 2011.[29] *"Policy makers should focus their efforts on further increasing the number and geographical distribution of physicians, particularly in more rural counties, where prescription opioid misuse is rapidly growing."*[29]

Jones et al. *"estimated national and state trends in opioid agonist medication-assisted treatment (OA-MAT) need and capacity to identify gaps and inform policy decisions."*[17] The authors concluded that *"Significant gaps between treatment need and capacity exist at the state and national levels. Strategies to increase the number of OA-MAT providers are needed."*[17]

Komaromy et al. report on a teleECHO clinic based at the University of New Mexico Health Sciences Center that is focused on treatment of substance use disorders and behavioral health disorders.[94] *"Project ECHO (Extension for Community Healthcare Outcomes) trains and mentors primary care providers (PCPs) in the care of patients with complex conditions. ECHO is a distance education model that connects specialists with numerous PCPs via simultaneous video link for the purpose of facilitating case-based learning."*[94] This is one example of a model that could be used to promote expansion of access to treatment in underserved areas. This project offered a *"2-hour Integrated Addictions and Psychiatry (IAP) TeleECHO Clinic focused on supporting PCP evaluation and treatment of SUDs and behavioral health disorders"* on a weekly basis, and *"has also been used to recruit physicians to participate in DATA-2000 buprenorphine waiver trainings."*[94] The authors report that *"New Mexico is near the top among US states in DATA-2000 buprenorphine-waivered physicians per capita, and it has had much more rapid growth in waivered physicians practicing in traditionally underserved areas compared with the rest of the United States since the initiation of the teleECHO clinic focused on SUDs in 2005."*[94]

During last month's DUR meeting, Dr. Scott Junkins, M.D. Medical Director of the University of Utah Pain Management Center, discussed his work with Project ECHO (Extension for Community Health-Care Outcomes). He mentioned that the program started in New Mexico for hepatitis. *"Project ECHO is a cost-free partnership between community providers and a University of Utah interdisciplinary team of professionals developed to treat chronic and complex disease in rural and underserved areas through the use of technology."* Apart from chronic pain, other clinical areas covered by the University of Utah Project ECHO include behavioral health, burn & soft tissue injury, gastrointestinal & liver care, hepatitis C virus, patient abuse, pregnancy care, stroke case review, and EMS/trauma case review.

‘‘*Project ECHO empowers community providers to:*

1. *Deliver specialty care to all who need it,*
2. *Provide meaningful, case-based continuing education, and*
3. *Disseminate learning and reinforce best practices in multiple medical disciplines."*

In the US, opioid abuse treatment is limited to specific settings and providers. Currently, different sites and providers for buprenorphine treatment is not an option apart from those covered earlier and possibly in States where a collaborative practice agreement between physicians and pharmacists is in place. In Maryland for example, a pilot program of collaborative practice agreement between physicians and pharmacists for the treatment of opioid-dependent patients was considered successful (high program retention rates and increased adherence) so it was implemented permanently as the first state-approved opioid use disorder drug therapy management protocol.[48,95] Pharmacist responsibilities included intake assessments, follow-up appointments, medication adherence education, monitored

medication outcomes, and diversion prevention.[48,95] *"The pharmacist debriefed with the physician and documented each interaction, allowing for efficient assessment completion. The physician appended notes, when applicable, and cosigned each patient's record. The pharmacist prevented diversion by gathering data from outside providers, pharmacies, and laboratories."*[95]

Fox et al. investigated attitudes of opioid users toward different potential sites for buprenorphine maintenance treatment and found that of 102 participants of the computer-based interviews, *"the most preferred potential site for BMT was a harm reduction agency (51%), whereas fewer preferred general medical clinics (13%), drug treatment programs (12%), or were not interested in BMT (25%)."*[96]

In other countries such as the UK, community pharmacy services for people with drug problems include needle exchange and dispensing treatment (methadone and buprenorphine) for drug misuse.[97] Attitudes vary between pharmacists and some feel that they are part of the addiction team. Some pharmacists also prescribe for opioid dependence.[97]

Place in therapy and potential criteria to be reviewed

Factors and limitations to consider:

- **"Medication-assisted treatment (MAT)** is a comprehensive approach that combines approved medications (currently, methadone, buprenorphine or naltrexone) with counseling and other behavioral therapies to treat patients with opioid use disorder."[1]
- **Prescribing and Access Restrictions:** Under the Drug Addiction Treatment Act (DATA 2000), qualified physicians may obtain a waiver allowing them to prescribe and/or dispense approved Schedule III-V medications for the treatment of opioid dependence (prescribed in a doctor's office; methadone can only be dispensed by federally regulated Opioid Treatment Programs; OTPs).[98,99] Prescribing of buprenorphine tablets for opioid dependence is limited to physicians who have met the qualification criteria and have received a DEA number (second DEA number) specific to prescribing this product that has a number beginning with an "X".[9,36] The prescriber may extend the intervals between visits if the patient regularly has negative urine toxicology screens and receives a stable dose of buprenorphine.[9] "Buprenorphine can be prescribed for, up to, a 30-day supply shortly after beginning treatment. In contrast, methadone patients must comply with treatment for two years to be eligible to receive a 30-day take-home dose."[99,100] "SAMHSA-certified opioid treatment programs (OTPs) also are allowed to offer buprenorphine, but only are permitted to dispense treatment."[18]
- **Naloxone content:** Because the buprenorphine single product contains no naloxone, it is preferred for use during induction only. Following induction, buprenorphine/naloxone combination agents are preferred when clinical use includes unsupervised administration because it contains naloxone that would deter abuse. The unsupervised administration of buprenorphine single product should be limited to patients who cannot tolerate naloxone (e.g. hypersensitive to naloxone).
- **Treatment setting:** Refer to ASAM guideline section. Also, "*Clinicians should observe patients in their offices during induction. However, home buprenorphine induction may be considered"* (only recommended if patient or prescribing physician is experienced with the use of buprenorphine).[46]
- **Induction:** "Prior to induction, consideration should be given to the type of opioid dependence (i.e., long- or short-acting opioid), the time since last opioid use, and the degree of level of opioid dependence."[101] To avoid precipitating withdrawal, it is recommended that induction should be undertaken when objective and clear signs of withdrawal are evident.[101]

- **Short-acting opioid dependence:** Both buprenorphine/naloxone sublingual film (Suboxone film) and buprenorphine single product are indicated and may be used during the induction period for short-acting opioids or heroin.[78,102,103] However, the other combination products are indicated for maintenance therapy for opioid dependence and should not be used for induction, and use otherwise could therefore be viewed as inappropriate use in terms of their FDA indications. "Initial treatment may begin using buprenorphine/naloxone sublingual film or buprenorphine sublingual monotherapy when signs of moderate opioid withdrawal appear and not less than 6 hours after last opioid use."[102] "The combination product, buprenorphine and naloxone, is preferred therapy over buprenorphine monotherapy for induction treatment (and stabilization/maintenance treatment) for short-acting opioid dependence (U.S. Department of Health and Human Services, 2005)."[78]
- **Methadone or long-acting opioid dependence:** Buprenorphine/naloxone combination product is not recommended for use during the induction period for long-acting opioids or methadone.[102] Lexicomp notes state that initial treatment should begin using buprenorphine monotherapy under supervision.[102] Buprenorphine single product: "There is little controlled experience with induction in patients on methadone or other long-acting opioids; consult expert physician experienced with this procedure."[78] "Patients should be switched to the combination product for maintenance and unsupervised therapy."[102]
- **Supervised administration:** It is recommended that treatment be initiated with supervised administration.
- **Period of induction/titration:** "Titrating dose to clinical effectiveness should be done as rapidly as possible to prevent undue withdrawal symptoms and patient drop-out during the induction period."[78] According to Lexicomp and the product label, induction is usually accomplished within 3-4 days and it is stated that buprenorphine plus naloxone replace buprenorphine typically after 2 days.[78,101] "In some studies, gradual induction over several days led to a high rate of drop-out of buprenorphine patients during the induction period."[101]
- **Unsupervised administration:** According to the product label, this is dependent on the patient's clinical stability, the security of the patient's home situation, and any other factors likely to affect the ability of the patient to manage supplies of take-home medication.[101]

- **Maintenance:** Buprenorphine combination products are preferred for maintenance treatment. The American Society of Addiction Medicine (ASAM) states that *"Buprenorphine doses after induction and titration should be, on average, ≥8 mg per day. However, if patients are continuing to use opioids, consideration should be given to increasing the dose by 4-8 mg (daily doses of 12-16 mg or higher). The FDA approves dosing to a limit of 24 mg per day, and there is limited evidence regarding the relative efficacy of higher doses. In addition, the use of higher doses may increase the risk of diversion."*[46] SAMHSA Advisory (Winter 2016) also states that dosages higher than 24 mg/6 mg buprenorphine/naloxone daily or 24 mg buprenorphine daily have not been demonstrated to provide a clinical advantage.[13,104,105]
  Probuphine implant is also indicated for the maintenance treatment and it is unique in the sense that it provides a constant, low-level dose of buprenorphine for six months versus daily administration of other products.[1]

Table 2. Comparison of maintenance treatment options

(Adapted from Lexicomp, FDA news release for implant, ASAM guidelines pocket guide, product labels, "Opioid dependence treatment and guidelines", SAMHSA documents, and several other references)[1,9,13,37,41,46,106-111]

	Methadone	***Buprenorphine Pill or film***	***Buprenorphine Implant (Probuphine)*** =>Also refer to buprenorphine pill or film information for general buprenorphine information	***Extended Release Naltrexone (Vivitrol IM)***
Pharmacology	Full agonist => greatest abuse potential (additional dosing result in greater receptor activation, increasing the risk of abuse and adverse effects)	Partial Agonist => some abuse potential (results in a plateau where no additional effect is observed with additional dosing)	Partial Agonist => some abuse potential (results in a plateau where no additional effect is observed with additional dosing)	Full Antagonist => no abuse potential (blocks opioids from binding to receptors=>prevents euphoric and other effects)
Pharmacokinetics	Highly variable inter-individual pharmacokinetics Long bi-phasic half-life High potential for accumulation: => delayed toxicity including respiratory depression => may take up to 10 days to reach steady-state serum levels.	Significant first-pass metabolism, but high lipid solubility so excellent sublingual bioavailability (onset: 30-60 minutes; peak: 90-100 minutes) Elimination half-life: 37 hours (naloxone 1.1 hour) Zubsolv sublingual tablets & Bunavail buccal film provide higher bioavailability (more buprenorphine enters bloodstream allowing for lower doses).[13] Equivalent buprenorphine exposure: One Bunavail 4.2 mg/0.7 mg buccal film is equivalent to one suboxone 8 mg/2 mg sublingual tablet.[13,108] One Zubsolv 5.7 mg/1.4 mg sublingual tablet is equivalent to one suboxone 8 mg/2 mg sublingual tablet.[13,107]	Both buprenorphine and naloxone are extensively metabolized by liver	Both buprenorphine and naloxone are extensively metabolized by liver
Controlled substance?	Yes	Yes	Yes	No
Indication	Detoxification and maintenance treatment of <u>opioid addiction</u> (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services. <u>Chronic Pain</u>	Treatment of <u>opioid dependence</u>. (<u>Note</u> that buprenorphine single product buccal film; Belbuca; the transdermal patch and injections are indicated for use in <u>pain management</u>).	Maintenance treatment of <u>opioid dependence</u> in patients who have achieved and sustained prolonged clinical stability on low to moderate doses (≤8 mg/day) of a transmucosal buprenorphine-containing product for 3 months or longer with no need for	<u>Opioid dependence</u>: For the blockade of the effects of exogenously administered opioids (for the prevention of relapse to opioid dependence, following opioid detoxification) <u>Alcohol dependence</u>: Treatment of alcohol dependence (in patients

	Methadone	***Buprenorphine Pill or film***	***Buprenorphine Implant (Probuphine)*** =>Also refer to buprenorphine pill or film information for general buprenorphine information	***Extended Release Naltrexone (Vivitrol IM)***
			supplemental dosing or adjustments	who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with Vivitrol)
Age	Adults (Manufacturers state that safety, efficacy, and pharmacokinetics not established in pediatric patients <18 years of age) Caution in elderly	Zubsolv, Bunavail: ≥16 years Buprenorphine sublingual tablets: safety and effectiveness not established in pediatric patients. Caution in elderly or debilitated patients	Adults (Safety and efficacy have not been established in patients <16 years and studies did not include patients >65 years old)	The safety and efficacy of VIVITROL have not been established in the pediatric population. The pharmacokinetics of VIVITROL have not been evaluated in a pediatric population.
Administration/ Convenience (could also affect adherence)	Daily (but duration often longer) by visiting a clinic daily High potency Flexible dosing (recent evidence (Cochrane review[12] & other review[112]) noted greater treatment retention and lower cost associated with methadone vs buprenorphine when using flexible dosing)	Daily, but can be given every 2 to 3 days as tolerated and can be filled at a local pharmacy (vs visiting a clinic daily) Advantage: dosing flexibility Films dissolve more quickly than tablets => advantage when monitored dose ingestion is indicated;[13,113] potentially enhanced patient satisfaction[114]	Implants (4) for 6 months, but needs to be done by a certified healthcare provider. Potential surgical complications (during insertion or removal): risk of implant migration, protrusion, expulsion, and nerve damage resulting from the procedure.	Every 4 weeks/once a month IM gluteal injection by healthcare provider (alternating buttocks) NOT IV or SubQ Advantage: verifiable dosing
Setting	Specially licensed OTP (advantage: high structure of delivery setting), until the patient receives take-home doses. Only licensed physicians who are DEA registered and who work at an OTP can order methadone for dispensing at the certified OTP or hospital. Nicholls et al.[9] mention long waiting lists for entry into methadone maintenance treatment.	Office-based or OTP (Advantage: low burden of OBOT delivery; simple pharmacy availability (any pharmacy can fill the prescription); increased accessibility to treatment and avoiding the stigma and other negative feelings associated with going to methadone clinic), requires "X" waiver to prescribe or the licensed physician needs to be DEA registered and work at an OTP.	Outpatient setting Prescription use of this product is limited under DATA. "All Healthcare Providers must successfully complete a live training program on the insertion and removal procedures and become certified in the PROBUPHINE REMS program, prior to performing insertions or prescribing PROBUPHINE implants."[41] (must successfully complete a live training program, and demonstrate procedural competency prior to inserting or removing the implants) Prerequisite for participating in live training program leading to	Any medical setting, requires injection by healthcare provider; can be prescribed by any healthcare provider who is licensed to prescribe medications (no special training required); can also be prescribed for purchase at a pharmacy (any pharmacy can fill the prescription).

	Methadone	***Buprenorphine Pill or film***	***Buprenorphine Implant (Probuphine)*** =>Also refer to buprenorphine pill or film information for general buprenorphine information	***Extended Release Naltrexone (Vivitrol IM)***
			certification: "Healthcare Provider must have performed at least one qualifying surgical procedure in the last 3 months. Qualifying procedures are those performed under local anesthesia using aseptic technique, and include, at a minimum, making skin incisions, or placing sutures *[see PROBUPHINE REMS"*[41] Closed Distribution – only to healthcare providers certified in the Probuphine REMS Program.[115]	
Adherence	Supervised and if compliant with treatment for 2 years, could receive a 30-day take-home dose.	May be lost or forgotten (if prescribed and not in OTP)	Can't be lost or forgotten vs. daily; long-acting which should improve adherence	Can't be lost or forgotten vs. daily; long-acting which should improve adherence/facilitate compliance
Abuse potential	Usually in OTP unless compliant for 2 years, could receive take-home methadone which could be stolen misused or abused.	Could be stolen/misused/abused	Unlikely to be stolen/misused/abused. Contains a significant amount of drug that could lead to accidental exposure or intentional misuse or abuse if implant comes out of skin. Patients should be seen during the first week after insertion and at least once-monthly thereafter for continued counseling and psychosocial support.	Unlikely; low diversion, no dependence
Most common adverse effects/Safety concerns	Sedation (especially early in treatment), constipation, QT prolongation Higher overdose incidence and mortality (1 of every 3 opioid-related deaths is associated with methadone ingestion).[116,117]	Lower extremity swelling, urinary hesitancy, constipation Appears to have a better safety profile (pending direct comparison studies) in cases of overdosing vs methadone[9] or with respect to QT prolongation[56] This may be an important factor to consider as more patients are treated in the primary care setting.[56]	Implant-site pain, itching, and redness, headache, depression, constipation, nausea, vomiting, back pain, toothache, and oropharyngeal pain	Injection site reactions, nausea, malaise, hepatic enzyme abnormalities

	Methadone	***Buprenorphine Pill or film***	***Buprenorphine Implant (Probuphine)*** =>Also refer to buprenorphine pill or film information for general buprenorphine information	***Extended Release Naltrexone (Vivitrol IM)***
Caution Co-occurring conditions & drug interactions (e.g. HIV & HCV)	Concurrent BZPs/alcohol/CNS depressants Overdosing Drug-drug interactions	Concurrent BZPs/alcohol/CNS depressants Compromised respiratory function Hepatic impairment (both buprenorphine and naloxone are extensively metabolized by liver)* Metabolized through CYP 3A4 isoenzyme so monitor doses if concomitant CYP3A4 inducers/inhibitors. Anti-retrovirals: Some potential interactions, but appear to be fewer interactions vs methadone possibly due to different route of absorption (sublingual or buccal); less competitive.[13,118] In most cases (efavirenz,[119] elvitegravir with cobicistat,[120] nevirapine,[121] ritonavir,[122] tipranavir[123]) the potential interaction is some pharmacokinetic effect where no dose adjustment is needed/unlikely to be needed. For some products there are recommendations for monitoring (i.e. darunavir-ritonavir[124]), to use with caution (i.e. delavirdine as long-term effects more than 7 days are unknown[119,125]), or potential dose adjustments (i.e. slower titration or dose reduction may be warranted for atazanvir due to potential increased buprenorphine concentrations, cognitive impairment and oversedation[105,125,126]).[13]	Potential serious complications from insertion and removal. Rare but serious complications including nerve damage and migration resulting in embolism and death may result from improper insertion. Incomplete insertions or infections may lead to protrusion or expulsion. Metabolized through CYP 3A4 isoenzyme so monitor doses if concomitant CYP3A4 inducers/inhibitors.	Precipitated withdrawal if given before opioid free washout period; may be severe enough to require hospitalization (opioid-free period of 7-10 days is recommended; Abstinence from opioids can be difficult for patients to achieve)

	Methadone	***Buprenorphine Pill or film***	***Buprenorphine Implant (Probuphine)*** =>Also refer to buprenorphine pill or film information for general buprenorphine information	***Extended Release Naltrexone (Vivitrol IM)***
		HCV medications: Appear to be no significant reactions		
Switching drugs	Methadone to buprenorphine: Better tolerated when on <30-40 mg of methadone Methadone to naltrexone: Must be completely withdrawn from opioids	Buprenorphine to methadone: No delay needed Buprenorphine to naltrexone: 7-14 days after last dose of buprenorphine	**Converting back to sublingual tablet:** On day of implant removal, resume buprenorphine treatment at previous sublingual dose.	Naltrexone to buprenorphine: Wait 30 days for ER naltrexone (one day for oral naltrexone) Naltrexone to methadone: Wait 30 days for ER naltrexone (one day for oral naltrexone). Use low initial dose of methadone.

OTP=Opioid Treatment Program

OBOT=Office-Based Opioid Treatment (provides medication on a prescribed weekly or monthly basis, and is limited to buprenorphine).

* ‘‘*Buprenorphine/naloxone products are not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. Because hepatic impairment results in a reduced clearance of naloxone to a much greater extent than buprenorphine, the doses of buprenorphine and naloxone in this fixed-dose combination product cannot be individually titrated. Therefore, patients with severe hepatic impairment will be exposed to substantially higher levels of naloxone than patients with normal hepatic function. This may result in an increased risk of precipitated withdrawal at the beginning of treatment (induction) and may interfere with buprenorphine’s efficacy throughout treatment. In patients with moderate hepatic impairment, the differential reduction of naloxone clearance compared to buprenorphine clearance is not as great as in subjects with severe hepatic impairment. Therefore, buprenorphine/naloxone products are not recommended for initiation of treatment (induction) in patients with moderate hepatic impairment due to the increased risk of precipitated withdrawal. However, buprenorphine/naloxone products may be used with caution for maintenance treatment in patients with moderate hepatic impairment who have initiated treatment on a buprenorphine product without naloxone. However, patients should be carefully monitored and consideration given to the possibility of naloxone interfering with buprenorphine’s efficacy.”*[108,127]

- **Duration of treatment:** "There is no recommended time limit for treatment"[46] and "the optimal duration of office-based buprenorphine remains unclear."[13] *"Discontinuation of buprenorphine therapy should be made based on clinical judgment and upon mutual agreement by the practitioner and patient."*[13] Also, "Buprenorphine taper and discontinuation is a slow process and close monitoring is recommended" (usually takes several months).[13,46] *"A patient who relapses to illicit use of opioids should resume MAT."*[13]
- **Co-occurring medical conditions:** Patients dependent on opioids often have co-occurring conditions e.g. HIV infection/AIDS and hepatitis B and C virus (HCV) infection.[13] Refer to the comparison table above and product labels for information regarding interactions with medications for these conditions. Other co-occurring medical conditions include tuberculosis, skin and soft tissue infections, syphilis and other sexually transmitted diseases, seizure disorders, valvular heart disease secondary to endocarditis, pulmonary hypertension secondary to talc granulomatosis, lymphedema, psudoaneurysms of the neck and groin secondary to thrombophlebitis, and renal insufficiency secondary to heroin-associated nephropathy.[53] *"Treating opioid addiction in patients with co-occurring medical conditions is likely to result in better outcomes for the co-occurring conditions than would be achieved if the opioid use were not treated."*[53]
- **Other Special Populations:** Some patient populations may require special consideration and follow-up when being treated with opioid dependence treatment agents: pediatric patients, geriatric patients, and patients with liver disease. Buprenorphine sublingual tablets: safety and effectiveness not established in pediatric patients.[128] Buprenorphine is pregnancy category C.[128] Methadone is preferred during pregnancy, and buprenorphine is an alternative option, but buprenorphine as a single agent remains the preferred formulation for pregnant patients before using the combination of buprenorphine and naloxone (Suboxone) due to lack of data (Suboxone). It has been reported that in clinical trials, the incidence of adverse events was higher in older subjects, and it should be used with caution in the elderly (eg, life-threatening respiratory depression). Also, "one postmarketing study found that elderly patients were more likely to suffer from confusion and drowsiness after buprenorphine as compared to younger patients."[78]
- **Who might need higher doses?** Authors of recent review of published evidence on doses of buprenorphine in 6 European countries found some supportive evidence of rapid induction with buprenorphine and benefits of higher doses, but could not find "useful guidance on dosing choices for groups with complex clinical scenarios."[129] This question was therefore answered by an expert group of physicians with experience in addiction care (based on clinical practice experience).[129] "*There was general agreement that treatment outcomes can be improved by optimising buprenorphine doses in specific subgroups. Specific groups in whom buprenorphine doses may be too low and who could have better outcomes with optimised dosing were identified on the basis of clinical practice experience. These groups include people with severe addiction, high tolerance to opioids, and psychiatric comorbidities. In these groups it is recommended to review dosing choices to ensure buprenorphine dosing is sufficient."*[129]
- **Efficacy:** Refer to guideline and efficacy sections
- **Adverse effects:** Refer to safety section
- **REMS:** Buprenorphine Transmucosal Products for Opioid Dependence (BTOD): Elements to Assure Safe Use; Implementation System; Medication Guide[78]
- **Duplication of therapy:** Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms
- **Diversion/Abuse:** Buprenorphine single product and when combined with naloxone can be diverted and abused, but the likelihood is much higher with the single product that does not contain naloxone as naloxone causes withdrawal symptoms in abusers who either inject or snort the drug.

ASAM guidelines recommend strategies/steps that could be taken to reduce the chance of buprenorphine diversion: "frequent office visits (weekly in early treatment), urine drug testing, including testing for buprenorphine and metabolites, and recall visits for pill counts."[46]

- **Inappropriate use:** refer to inappropriate use section on page 8 and "Conditions and Circumstances That May Preclude a Patient as a Candidate for Office-Based Buprenorphine Treatment" (based on TIP 40 on page 14)
- **DATA-certified physicians in Utah:** SAMHSA tracks the number of DATA-certified physicians by state who are eligible to provide buprenorphine treatment for opioid dependency and the information for Utah is shown below for the last 3 years (excerpt):

  "Year: 2016 | **State:** Utah
  Certified Physicians with 30 Patients: 41
  Certified Physicians with 100 Patients: 18

  Year: 2015 | **State:** Utah
  Certified Physicians with 30 Patients: 47
  Certified Physicians with 100 Patients: 23

  Year: 2014 | **State:** Utah
  Certified Physicians with 30 Patients: 31
  Certified Physicians with 100 Patients: 7"[130]

- **Opioid treatment programs in Utah[131]** (Refer to SAMHSA website for additional information):

Program Name	City
Metro Treatment of Utah, LP	Bountiful
Discovery House-LT, Inc.	Layton
Metamorphosis Salt Lake City, Inc.	Murray
Metamorphosis, Ogden, Inc.	Ogden
Discovery House UC, Inc.	Orem
True North Treatment Center	Orem
Utah County Treatment Program of Project Reality	Provo
Discovery House- Utah Inc.	Salt Lake City
Tranquility Place	Salt Lake City
De Novo Services LLC	Salt Lake City
Project Reality	Salt Lake City
BrookStone Medical Center, LLC	ST George
Metro Treatment of Utah, LP	St. George
Discovery House-TV, Inc.	Taylorsville

SAMHSA Advisory (Winter 2016)[13] also covers topics such as:

- **Behavioral treatment**
- **Informed consent and treatment agreements**
- **Monitoring of Adherence and Response to treatment**

Utah Medicaid Utilization Data

BUPRENORPHINE OPIOID ABUSE DETERRENTS - ALL CLAIMS

		2013		2014		2015		2016*		ALL	
GENERIC	**DESCRIPTION**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**
Buprenorphine HCl	Buprenorphine Sublingual Tablet	203	41	241	54	234	61	284	62	962	172
Buprenorphine HCl	Probuphine Subcutaneous Implant	0	0	0	0	0	0	0	0	0	0
Buprenorphine HCl	Subutex Sublingual Tablet	0	0	0	0	0	0	0	0	0	0
Buprenorphine HCl-Naloxone HCl Dihydrate	Bunavail Buccal Film Strip	0	0	0	0	0	0	5	2	5	2
Buprenorphine HCl-Naloxone HCl Dihydrate	Buprenorphine-Naloxone Sublingual Tablet	4	2	4	2	5	3	4	3	17	9
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	4,360	617	4,824	727	4,698	706	3,517	572	17,399	1,621
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Tablet	1,124	260	2	1	0	0	0	0	1,126	261
Buprenorphine HCl-Naloxone HCl Dihydrate	Zubsolv Sublingual Tablet	0	0	58	13	192	30	195	33	445	56
	TOTALS	**5,691**	**721**	**5,129**	**761**	**5,129**	**762**	**4,005**	**647**	**19,954**	**1,809**

BUPRENORPHINE OPIOID ABUSE DETERRENTS - ACO CLAIMS

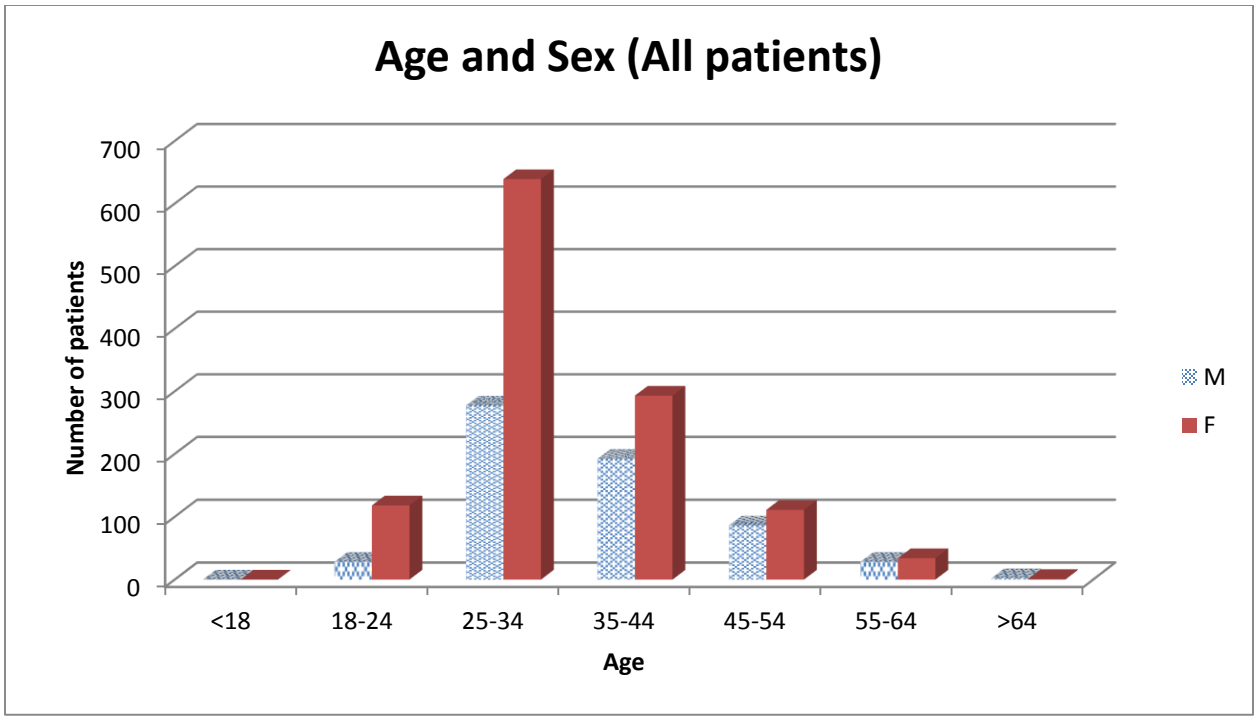
		2013		2014		2015		2016*		ALL	
GENERIC	**DESCRIPTION**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**
Buprenorphine HCl	Buprenorphine Sublingual Tablet	157	35	177	39	171	46	233	52	738	139
Buprenorphine HCl	Probuphine Subcutaneous Implant	0	0	0	0	0	0	0	0	0	0
Buprenorphine HCl	Subutex Sublingual Tablet	0	0	0	0	0	0	0	0	0	0

BUPRENORPHINE OPIOID ABUSE DETERRENTS -
ACO CLAIMS

		2013		2014		2015		2016*		ALL	
GENERIC	**DESCRIPTION**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**
Buprenorphine HCl-Naloxone HCl Dihydrate	Bunavail Buccal Film Strip	0	0	0	0	0	0	3	1	3	1
Buprenorphine HCl-Naloxone HCl Dihydrate	Buprenorphine-Naloxone Sublingual Tablet	4	2	3	2	5	3	4	3	16	9
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	3,027	464	3,291	513	3,248	526	2,388	412	11,954	1,209
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Tablet	819	203	0	0	0	0	0	0	819	203
Buprenorphine HCl-Naloxone HCl Dihydrate	Zubsolv Sublingual Tablet	0	0	55	11	169	22	145	24	369	40
	TOTALS	**4,007**	**549**	**3,526**	**538**	**3,593**	**566**	**2,773**	**473**	**13,899**	**1,358**

BUPRENORPHINE OPIOID ABUSE DETERRENTS -
FFS CLAIMS

		2013		2014		2015		2016*		ALL	
GENERIC	**DESCRIPTION**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**
Buprenorphine HCl	Buprenorphine Sublingual Tablet	46	14	64	20	63	25	51	17	224	68
Buprenorphine HCl	Probuphine Subcutaneous Implant	0	0	0	0	0	0	0	0	0	0
Buprenorphine HCl	Subutex Sublingual Tablet	0	0	0	0	0	0	0	0	0	0
Buprenorphine HCl-Naloxone HCl Dihydrate	Bunavail Buccal Film Strip	0	0	0	0	0	0	2	1	2	1
Buprenorphine HCl-Naloxone HCl Dihydrate	Buprenorphine-Naloxone Sublingual Tablet	0	0	1	1	0	0	0	0	1	1
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	1,333	207	1,533	273	1,450	248	1,129	198	5,445	651
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Tablet	305	79	2	1	0	0	0	0	307	80
Buprenorphine HCl-Naloxone HCl Dihydrate	Zubsolv Sublingual Tablet	0	0	3	2	23	10	50	10	76	19
	TOTALS	**1,684**	**258**	**1,603**	**290**	**1,536**	**275**	**1,232**	**221**	**6,055**	**756**

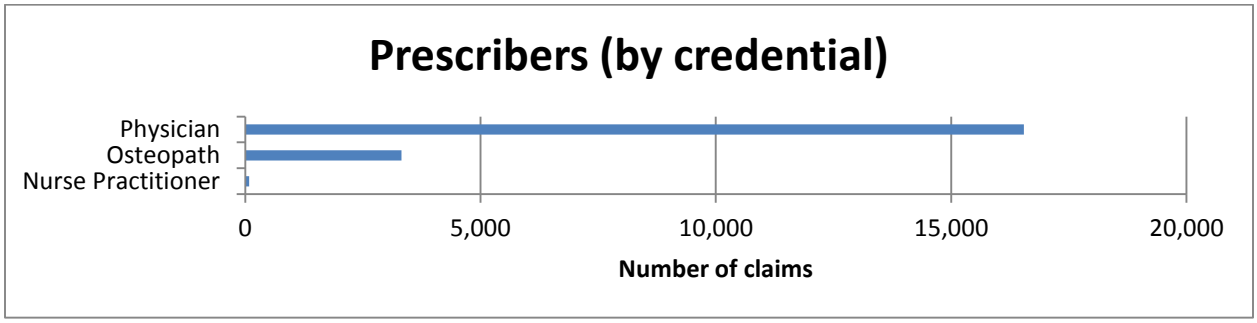


TOTAL PATIENTS 2013-2016

AGE*	M	F	Total
<18	0	0	0
18-24	28	118	146
25-34	277	639	916
35-44	192	293	485
45-54	86	111	197
55-64	28	34	62
>64	2	1	3
TOTAL	613	1,196	

* Age at first claim.

a) ALL (ACO & FFS)



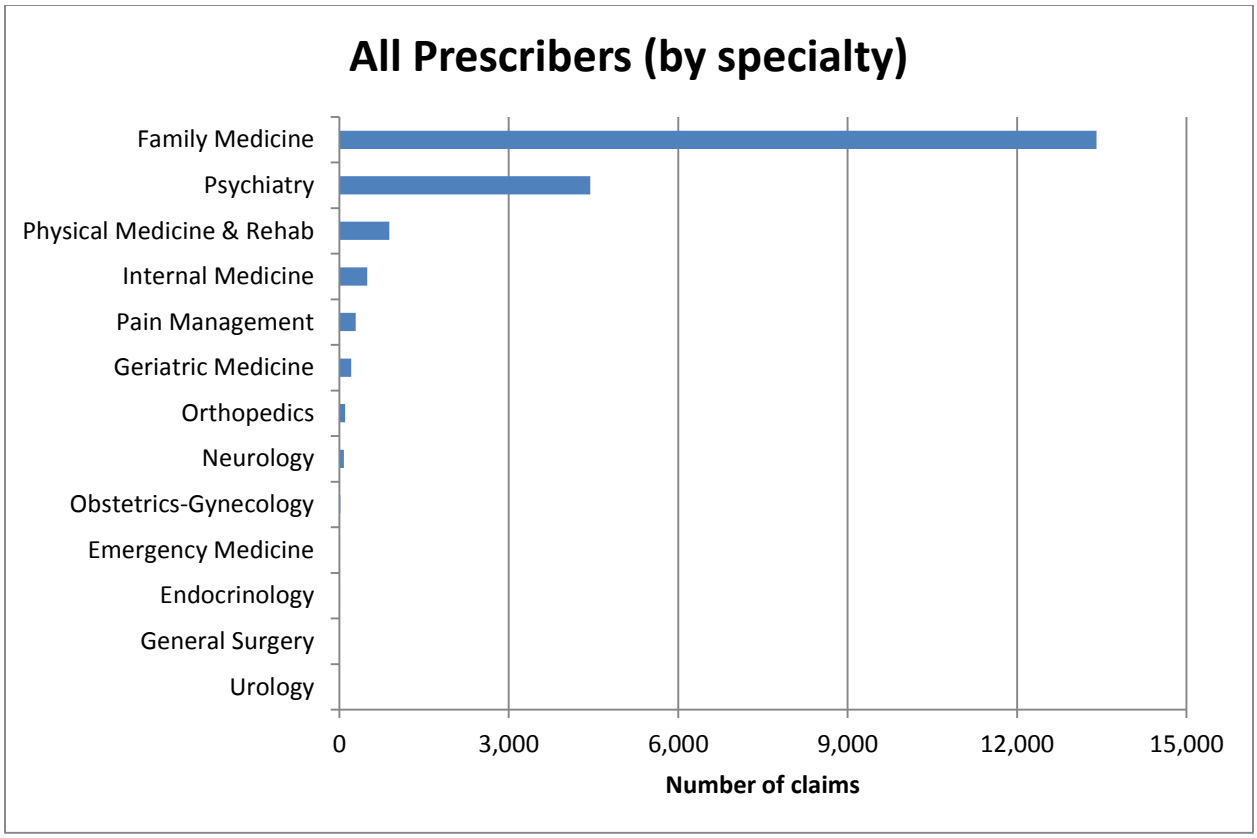
BUPRENORPHINE OPIOID ABUSE DETERRENTS PRESCRIBER TYPE	TOTAL CLAIMS 2013-16	
Nurse Practitioner	83	0.42%
Osteopath	3,324	16.66%
Physician	16,547	82.93%
TOTAL CLAIMS	**19,954**	

b) ACO

BUPRENORPHINE OPIOID ABUSE DETERRENTS PRESCRIBER TYPE	TOTAL CLAIMS 2013-16	
Nurse Practitioner	30	0.22%
Osteopath	1,775	12.77%
Physician	12,094	87.01%
TOTAL CLAIMS	**13,899**	

c) FFS

BUPRENORPHINE OPIOID ABUSE DETERRENTS PRESCRIBER TYPE	TOTAL CLAIMS 2013-16	
Nurse Practitioner	53	0.88%
Osteopath	1,549	25.58%
Physician	4,453	73.54%
TOTAL CLAIMS	**6,055**	



BUPRENORPHINE OPIOID ABUSE DETERRENTS PRESCRIBER SPECIALTY	TOTAL CLAIMS 2013-16	
Urology	1	0.01%
General Surgery	3	0.02%
Endocrinology	10	0.05%
Emergency Medicine	11	0.06%
Obstetrics-Gynecology	18	0.09%
Neurology	79	0.40%
Orthopedics	103	0.52%
Geriatric Medicine	211	1.06%
Pain Management	290	1.45%
Internal Medicine	495	2.48%
Physical Medicine & Rehab	883	4.43%
Psychiatry	4,445	22.28%
Family Medicine	13,405	67.18%
TOTAL CLAIMS	**19,954**	

BUPRENORPHINE OPIOID ABUSE DETERRENTS ACO PRESCRIBER SPECIALTY	TOTAL CLAIMS 2013-16	
Urology	1	0.01%
General Surgery	1	0.01%
Obstetrics-Gynecology	2	0.01%
Endocrinology	7	0.05%
Emergency Medicine	10	0.07%
Neurology	63	0.45%
Orthopedics	92	0.66%
Geriatric Medicine	128	0.92%
Pain Management	244	1.76%
Internal Medicine	263	1.89%
Physical Medicine & Rehab	825	5.94%
Psychiatry	3,414	24.56%
Family Medicine	8,849	63.67%
TOTAL CLAIMS	**13,899**	

BUPRENORPHINE OPIOID ABUSE DETERRENTS FFS PRESCRIBER SPECIALTY	TOTAL CLAIMS 2013-16	
Emergency Medicine	4	0.07%
General Surgery	2	0.03%
Endocrinology	8	0.13%
Orthopedics	11	0.18%
Obstetrics-Gynecology	8	0.13%
Neurology	16	0.26%
Pain Management	46	0.76%
Physical Medicine & Rehab	58	0.96%
Geriatric Medicine	83	1.37%
Internal Medicine	232	3.83%
Psychiatry	1,031	17.03%
Family Medicine	4,556	75.24%
TOTAL CLAIMS	**6,055**	

A report regarding the buprenorphine prescribing practices and exposures reported to a poison center in Utah (2002-2011) stated that the annual number of prescribers writing prescriptions for buprenorphine increased 67-fold (16 in 2002 when buprenorphine was approved by the FDA to 1088 in 2011) and the annual filling of prescriptions increased 444-fold (22 to 9793). It was also reported that the number of exposures increased 13-fold (6 to 81) and these were primarily among adults aged ≥20 years and children aged ≤5 years. There were 3 fatal cases out of 462 reported (<1%). The authors report the implications for public health practice that nontherapeutic use (misuse and unintentional exposure) can have adverse outcomes. They also report that expanded use of buprenorphine for opioid dependence is important to improve public health, and that education and counseling could help to reduce adverse effects.

Upon reviewing the prescriber types and maximum daily dose data (table on next page, and appendix 5), it is important to consider whether off-label prescribing may be an issue (i.e. is it being used for treatment of pain?).

BUPRENORPHINE OPIOID ABUSE DETERRENTS - ALL CLAIMS		Number of Unique Patients with a Maximum Average Daily Dose (ADD) of:				ADD >32 mg	
GENERIC	DESCRIPTION	< 17 mg	17 - 24 mg	25 - 32 mg	> 32 mg	ACO	FFS
Buprenorphine HCl	Buprenorphine Sublingual Tablet	126	33	8	5	5	0
Buprenorphine HCl	Probuphine Subcutaneous Implant	0	0	0	0	0	0
Buprenorphine HCl	Subutex Sublingual Tablet	0	0	0	0	0	0
Buprenorphine HCl-Naloxone HCl Dihydrate	Bunavail Buccal Film Strip	2	0	0	0	0	0
Buprenorphine HCl-Naloxone HCl Dihydrate	Buprenorphine-Naloxone Sublingual Tablet	5	2	1	1	1	0
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	1,100	396	57	68	42	26
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Tablet	170	71	8	12	12	0
Buprenorphine HCl-Naloxone HCl Dihydrate	Zubsolv Sublingual Tablet	37	18	0	1	0	1

GENERIC	DESCRIPTION	< 8.4 mg	8.4 - 12.6 mg	> 12.6 mg
Buprenorphine HCl-Naloxone HCl Dihydrate	Bunavail Buccal Film Strip	1	1	0

					ADD >17.2 mg	
GENERIC	DESCRIPTION	< 11.4 mg	11.4 - 17.2 mg	> 17.2 mg	ACO	FFS
Buprenorphine HCl-Naloxone HCl Dihydrate	Zubsolv Sublingual Tablet	15	31	10	7	3

Conclusions

Current clinical practice guidelines recommend methadone or combination buprenorphine/naloxone as first-line opioid agonist treatment agents in opioid dependence. According to guideline recommendations, opioid dependence treatment plans should include participation in a comprehensive program including psychological therapy in addition to maintenance on an opioid agonist agent. The selection of an opioid dependence treatment agent should be guided by the individual patient's disease history and personal preference in combination with the provider's assessment of the immediate and chronic effects of therapy and overall health status of the patient.

The buprenorphine products indicated in the treatment of opioid dependence are effective treatment options when used and monitored properly.[13,14] If buprenorphine is selected as treatment, the buprenorphine-naloxone combination product is the preferred and recommended option (formulated to be less subject to diversion as naloxone produces an antagonist effect when crushed and used via the nasal or intravenous route) apart from patients who may be allergic or intolerant to naloxone or those who are pregnant who may need to use the single buprenorphine product beyond the induction period.[13,42] Use of these opioid dependence buprenorphine treatment agents in pain is off-label and not recommended.[40,128]

The dose of buprenorphine/naloxone should be *"adjusted to a level that holds the patient in treatment and suppresses opioid withdrawal effects"* and this optimal maintenance dose will vary between patients, but dosages higher than 24 mg/6 mg (or 24 mg buprenorphine) have not been demonstrated to provide a clinical advantage.[13,104]

Guidelines do not currently recommend one buprenorphine/naloxone combination agent over another or recommend a specific duration of treatment. The buprenorphine/naloxone combination agents are not recommended in the initial detoxification of patients using long-acting opioids, as it may increase risk and severity of withdrawal symptoms.[19] Buprenorphine single agent (sublingual) is preferred for induction in these patients, and the buprenorphine/naloxone combination agent (Suboxone) is generally initiated after two days of buprenorphine single agent (sublingual) titration.[40] Probuphine is indicated in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing products.[41]

The Utah Medicaid Data indicates potential inappropriate use of buprenorphine sublingual/buccal agents. Whilst the recently announced expanded access to buprenorphine treatment (July 2016 by HHS) could help reduce opioid and heroin overdoses, it could also result in more diversion to ease withdrawal symptoms in addicts (as a street drug) or by "white collar professionals" that choose to treat their addiction on their own (not through a medical provider).[48,132] All parties involved have a responsibility to ensure appropriate use of buprenorphine.

Appendix 1 – Drug information

Table 3. Buprenorphine Opioid Dependence Treatment Agents[13,37]

Product	Route of Administration	Available Doses	Dose Range (mg), Adults
"**Note:** The combination product, buprenorphine and naloxone, is preferred therapy over buprenorphine monotherapy for induction treatment (and stabilization/maintenance treatment) for short-acting opioid dependence (US Department of Health and Human Services 2005)."			
Buprenorphine (Generic) (Subutex discontinued[133])	Sublingual tablet	2 mg, 8 mg	**Induction:** Day 1: 8 mg; Day 2 and subsequent induction days: 16 mg **Maintenance:** Target dose: 16 mg/day; in some patients 12 mg/day may be effective; patients should be switched to the buprenorphine/naloxone combination product for maintenance and unsupervised therapy Range: 4 mg to 24 mg*
Buprenorphine (Probuphine)	Subcutaneous implant	Kit: 74.2 mg (4)	Insert 4 implants subdermally in the inner side of the upper arm. Remove no later than 6 months after the date of insertion; if continued treatment is desired, insert 4 new implants subdermally in the inner side of the contralateral arm. After one insertion in each arm, discontinue treatment with subdermal implants. **Converting back to sublingual tablet:** On day of implant removal, resume buprenorphine treatment at previous sublingual dose.
"Notes: Buprenorphine/naloxone is not recommended for use during the induction period for long-acting opioids or methadone; initial treatment should begin using buprenorphine monotherapy under supervision. Patients should be switched to the combination product for maintenance and unsupervised therapy. Initiate treatment with sublingual buprenorphine/naloxone or buprenorphine monotherapy during the induction period for short-acting opioids or heroin; initiate treatment when signs of moderate opioid withdrawal appear and not less than 6 hours after last opioid use. Titrate to adequate maintenance dose as rapidly as possible based on control of acute withdrawal symptoms."			

Product	Route of Administration	Available Doses	Dose Range (mg), Adults
Buprenorphine and Naloxone (Generic; Zubsolv®)	Sublingual tablet	Buprenorphine/ Naloxone: Generic: 2 mg/0.5 mg 8 mg/2 mg Zubsolv: 1.4 mg/0.36 mg 2.9 mg/0.71 mg 5.7 mg/1.4 mg	**Induction: Heroin or other short-acting opioid dependency: Sublingual:** **Sublingual tablet (Zubsolv):** *Day 1 induction dose:* Initial: Sublingual: Buprenorphine 1.4 mg/naloxone 0.36 mg: May titrate dose, based on control of acute withdrawal symptoms in increments of buprenorphine 1.4 mg/naloxone 0.36 mg or buprenorphine 2.9 mg/naloxone 0.71 mg every 1.5 to 2 hours to a total day 1 dose up to buprenorphine 5.7 mg/naloxone 1.4 mg. Some patients (eg, those with recent exposure to buprenorphine) may tolerate up to buprenorphine 4.2 mg/naloxone 1.08 mg as a single, second dose. *Day 2 induction dose:* Up to buprenorphine 11.4 mg/naloxone 2.9 mg once daily. **Maintenance:** **Sublingual tablet (generic 2 mg/0.5 mg or 8 mg/2 mg):** Target dose: Buprenorphine 16 mg/naloxone 4 mg once daily Dosage should be adjusted in increments/decrements of buprenorphine 2 mg/naloxone 0.5 mg or buprenorphine 4 mg/naloxone 1 mg to a level that maintains treatment and suppresses opioid withdrawal symptoms Usual range: Buprenorphine 4 to 24 mg/naloxone 1 to 6 mg once daily **Sublingual tablet (Zubsolv):** Target dose: Buprenorphine 11.4 mg/naloxone 2.9 mg once daily Dosage should be adjusted in increments/decrements of buprenorphine 1.4 mg/naloxone 0.36 or buprenorphine 2.9 mg/naloxone 0.71 mg to a level that maintains treatment and suppresses opioid withdrawal symptoms Usual range: Buprenorphine 2.9 to 17.2 mg/naloxone 0.71 to 4.2 mg once daily

Product	Route of Administration	Available Doses	Dose Range (mg), Adults
Buprenorphine and Naloxone (Bunavail®)	Buccal film	Buprenorphine/ Naloxone: 2.1 mg/0.3 mg 4.2 mg/0.7 mg 6.3 mg/1 mg	**Maintenance:** Target dose: Buprenorphine 8.4 mg/naloxone 1.4 mg once daily; dosage should be adjusted in increments/decrements of buprenorphine 2.1 mg/naloxone 0.3 mg to a level that maintains treatment and suppresses opioid withdrawal symptoms Usual range: Buprenorphine 2.1 to 12.6 mg/naloxone 0.3 to 2.1 mg once daily
Buprenorphine and Naloxone (Suboxone®)	Sublingual film	Buprenorphine/ Naloxone: 2 mg/0.5 mg 4 mg/1 mg 8 mg/2 mg 12 mg/3 mg	**Induction:** *Day 1:* Initial: Sublingual: Buprenorphine 2 mg/naloxone 0.5 mg or buprenorphine 4 mg/naloxone 1 mg; may titrate dose, based on control of acute withdrawal symptoms, in buprenorphine 2 mg/naloxone 0.5 mg or buprenorphine 4 mg/naloxone 1 mg increments approximately every 2 hours up to a total dose of buprenorphine 8 mg/naloxone 2 mg. *Day 2:* Up to buprenorphine 16 mg/naloxone 4 mg once daily. **Maintenance:** Sublingual or buccal: Target dose: Buprenorphine 16 mg/naloxone 4 mg once daily; Dosage should be adjusted in increments/decrements of buprenorphine 2 mg/naloxone 0.5 mg or buprenorphine 4 mg/naloxone 1 mg to a level that maintains treatment and suppresses opioid withdrawal symptoms Usual range: Buprenorphine 4 to 24 mg/naloxone 1 to 6 mg once daily*

* Dosages higher than 24 mg buprenorphine per day and 24 mg/6 mg buprenorphine/naloxone per day have not been demonstrated to provide a clinical advantage[13,104,105]

Appendix 2 – Pharmacology

The opioid analgesics bind to specific receptors within and outside the central nervous system (CNS).[83,84] Three opioid receptors are indicated in the mechanism of opioid analgesia: mu, delta, and kappa. The mu receptor is considered the most important and its activation produces both analgesic and euphoric effects. Mu receptors are found within the CNS and peripherally in areas and tracts associated with pain perception, sensory nerves, mast cells, and in the gastrointestinal (GI) tract.[83,84] The activation is highly variable and the response seen between patients and the various opioids therefore vary. Factors such as renal and hepatic function, age and genetic factors also affect an individual's response to opioids.[134,135]

Opioids are classified as full agonists, partial agonists, or mixed agonist-antagonists. Full agonists' effectiveness with increasing doses is not limited by a ceiling and they will not reverse or antagonize the effects of other full agonists given simultaneously. Morphine, hydromorphone, codeine, oxycodone, oxymorphone, hydrocodone, methadone, levorphanol, fentanyl and heroin are classified as full agonists. Mixed agonist-antagonists block or are neutral at one opioid receptor while activating a different opioid receptor and their analgesic effectiveness is also limited by a dose-related ceiling effect. Examples include pentazocine (Talwin), butorphanol tartrate (Stadol), dezocine (Dalgan), and nalbuphine hydrochloride (Nubain). They are contraindicated for use in patients receiving an opioid agonist because they may precipitate a withdrawal syndrome and increase pain. Partial agonists (such as buprenorphine) are subject to a ceiling effect and are less effective analgesics than full agonists at opioid receptors.[136] "*This "ceiling effect" lowers the risk of misuse, dependency, and side effects."*[18]

Buprenorphine is used as a parenteral analgesic for acute pain and as a transdermal analgesic for chronic pain.[81,86] Buprenorphine has poor oral bioavailability which is improved when used via the sublingual and buccal routes. Both sublingual and buccal buprenorphine formulations have been developed for the treatment of opioid dependence. When used via the sublingual and buccal routes, buprenorphine therapy is associated with less risk of abuse as the rate at which it enters the bloodstream is still significantly reduced compared to parenteral administration.[44] The addition of naloxone further reduces the risk of diversion and abuse. Naloxone is associated with poor bioavailability when given via the sublingual route and good bioavailability when given via the nasal or parenteral route, resulting in little to no effects when used sublingually and opioid withdrawal symptoms when used via other routes of administration.[137]

Appendix 3 – Buprenorphine Waiver Management

Excerpts from SAMHSA Buprenorphine Waiver Management[138]

"The Drug Addiction Treatment Act of 2000 (DATA 2000) expands the clinical context of medication-assisted opioid dependency treatment. Qualified physicians are permitted to dispense or prescribe specifically approved Schedule III, IV, and V narcotic medications (medications that have a lower risk for abuse, like buprenorphine) in settings other than an opioid treatment program (OTP) such as a methadone clinic. OTPs provide medication-assisted treatment (MAT) for people diagnosed with an opioid use disorder.
In addition, DATA 2000 reduces the regulatory burden on physicians who choose to practice opioid dependency treatment by permitting qualified physicians to apply for and receive waivers of the special registration requirements defined in the Controlled Substances Act."[138]

Waiver Process and Required Training
"In order to prescribe or dispense buprenorphine, physicians must qualify for a physician waiver, which includes completing eight hours of required training, and applying for a physician waiver. Physicians can complete the Online Request for Patient Limit Increase.
Physicians are also required to complete buprenorphine training and provide their training certificate after completing the Waiver Notification Form.
These waiver applications are forwarded to the DEA, which assigns the physician a special identification number. DEA regulations require this number to be included on all buprenorphine prescriptions for opioid dependency treatment, along with the physician's regular DEA registration number."[138]

Buprenorphine Pharmacy Lookup
"Pharmacists should go to the Buprenorphine Pharmacy Lookup to verify a physician's certification for buprenorphine."[138]

Training, Publications, and Other Resources
"SAMHSA's Division of Pharmacologic Therapies (DPT) provides the required buprenorphine training for physicians and other training materials and resources for MAT professionals."[138]

Please refer to the SAMHSA website for complete information and additional requirements e.g. record keeping requirements, etc.

Excerpt from SAMHSA Advisory (Winter 2016)

"To qualify, a physician must hold a valid medical license, be registered with the DEA, be capable of referring patients to counseling and other services, and meet at least one of the following criteria:

- *Hold a subspecialty board certification in addiction medicine or addiction psychiatry*
- *Have completed not less than 8 hours of approved training*
- *Have participated as an investigator in one or more clinical trials leading to the approval of a narcotic drug in Schedules III, IV, or V for maintenance or detoxification treatment*
- *Have experience or training deemed by his or her state medical licensing board or the U.S. Department of Health and Human Services to demonstrate the ability to treat and manage opioid dependence."[13,138]*

Appendix 4 – Systematic Reviews

Cochrane Reviews

Author(s)	Title	Objectives	Main Results	Author's Conclusions
Mattick RP, et al. (2014) (Searched databases to January 2013)[12]	Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence	"To evaluate buprenorphine maintenance compared to placebo and to methadone maintenance in the management of opioid dependence, including its ability to retain people in treatment, suppress illicit drug use, reduce criminal activity, and mortality."	"We include 31 trials (5430 participants), the quality of evidence varied from high to moderate quality. There is high quality of evidence that buprenorphine was superior to placebo medication in retention of participants in treatment at all doses examined. Specifically, buprenorphine retained participants better than placebo: at low doses (2 - 6 mg), 5 studies, 1131 participants, risk ratio (RR) 1.50; 95% confidence interval (CI) 1.19 to 1.88; at medium doses (7 - 15 mg), 4 studies, 887 participants, RR 1.74; 95% CI 1.06 to 2.87; and at high doses (≥ 16 mg), 5 studies, 1001 participants, RR 1.82; 95% CI 1.15 to 2.90. However, there is moderate quality of evidence that only high-dose buprenorphine (≥ 16 mg) was more effective than placebo in suppressing illicit opioid use measured by urinanalysis in the trials, 3 studies, 729 participants, standardised mean difference (SMD) -1.17; 95% CI -1.85 to -0.49, Notably, low-dose, (2 studies, 487 participants, SMD 0.10; 95% CI -0.80 to 1.01), and medium-dose, (2 studies, 463 participants, SMD -0.08; 95% CI -0.78 to 0.62) buprenorphine did not suppress illicit opioid use measured by urinanalysis better than placebo. There is high quality of evidence that buprenorphine in flexible doses adjusted to participant need,was less effective than methadone in retaining participants, 5 studies, 788 participants, RR 0.83; 95% CI 0.72 to 0.95. For those retained in treatment, no difference was observed in suppression of opioid use as measured by urinalysis, 8 studies, 1027 participants, SMD -0.11; 95% CI -0.23 to 0.02 or self report, 4 studies, 501 participants, SMD -0.11; 95% CI -0.28 to 0.07, with moderate quality of evidence. Consistent with the results in the flexible-dose studies, in low fixed-dose studies, methadone (≤ 40 mg) was more likely to retain participants than low-dose buprenorphine (2 - 6 mg), (3 studies, 253 participants, RR 0.67; 95% CI: 0.52 to 0.87). However, we found contrary results at medium dose and high dose: there was no difference between medium-dose buprenorphine (7 - 15 mg) and medium-dose methadone (40 - 85 mg) in retention, (7 studies, 780 participants, RR 0.87; 95% CI 0.69 to 1.10) or in suppression of illicit opioid use as measured by urines, (4 studies, 476 participants, SMD 0.25; 95% CI -0.08 to 0.58) or self report of illicit opioid use, (2 studies, 174 participants, SMD -0.82; 95% CI -1.83	"Buprenorphine is an effective medication in the maintenance treatment of heroin dependence, retaining people in treatment at any dose above 2 mg, and suppressing illicit opioid use (at doses 16 mg or greater) based on placebo-controlled trials. However, compared to methadone, buprenorphine retains fewer people when doses are flexibly delivered and at low fixed doses. If fixed medium or high doses are used, buprenorphine and methadone appear no different in effectiveness (retention in treatment and suppression of illicit opioid use); however, fixed doses are rarely used in clinical practice so the flexible dose results are more relevant to patient care. Methadone is superior to buprenorphine in retaining people in treatment, and methadone equally suppresses illicit opioid use."

Author(s)	Title	Objectives	Main Results	Author's Conclusions
			to 0.19). Similarly, there was no difference between high-dose buprenorphine (≥ 16 mg) and high-dose methadone (≥ 85 mg) in retention (RR 0.79; 95% CI 0.20 to 3.16) or suppression of self-reported heroin use (SMD -0.73; 95% CI -1.08 to -0.37) (1 study, 134 participants). Few studies reported adverse events; two studies compared adverse events statistically, finding no difference between methadone and buprenorphine, except for a single result indicating more sedation among those using methadone."	
	Additional Information from Abstract "Background Buprenorphine maintenance treatment has been evaluated in randomised controlled trials against placebo medication, and separately as an alternative to methadone for management of opioid dependence."			
Minozzi S, et al. (2014)[71] (Searched databases to January 2014)	Detoxification treatments for opiate dependent adolescents	"To assess the effectiveness of any detoxification treatment alone or in combination with psychosocial intervention compared with no intervention, other pharmacological intervention or psychosocial interventions on completion of treatment, reducing the use of substances and improving health and social status."	"Two trials involving 190 participants were included. One trial compared buprenorphine with clonidine for detoxification. No difference was found for drop out: risk ratio (RR) 0.45 (95% confidence interval (CI): 0.20 to 1.04) and acceptability of treatment: withdrawal score mean difference (MD): 3.97 (95% CI -1.38 to 9.32). More participants in the buprenorphine group initiated naltrexone treatment: RR 11.00 (95% CI 1.58 to 76.55), quality of evidence moderate. The other trial compared maintenance treatment versus detoxification treatment: buprenorphine-naloxone maintenance versus buprenorphine detoxification. For drop out the results were in favour of maintenance treatment: RR 2.67 (95% CI 1.85, 3.86), as well as for results at follow-up RR 1.36 [95% CI 1.05to 1.76); no differences for use of opiate, quality of evidence low."	"It is difficult to draw conclusions on the basis of two trials with few participants. Furthermore, the two studies included did not consider the efficacy of methadone that is still the most frequent drug utilised for the treatment of opioid withdrawal. One possible reason for the lack of evidence could be the difficulty in conducting trials with young people due to practical and ethical reasons."
	"Background The scientific literature examining effective treatments for opioid dependent adults clearly indicates that pharmacotherapy is a necessary and acceptable component of effective treatments for opioid dependence. Nevertheless, no studies have been published that systematically assess the effectiveness of the pharmacological detoxification among adolescents."			
Nielsen S, et al. (2016)[57]	Opioid agonist treatment for	"To assess the effects of maintenance	"We identified six randomised controlled trials that met inclusion criteria (607 participants).	"There was low to moderate quality evidence supporting the use of maintenance

Author(s)	Title	Objectives	Main Results	Author's Conclusions
(Searches to 2014 and 2015 depending on databases searched)	pharmaceutical opioid dependent people	agonist pharmacotherapy for the treatment of pharmaceutical opioid dependence."	We found moderate quality evidence from two studies of no difference between methadone and buprenorphine in self reported opioid use (risk ratio (RR) 0.37, 95% confidence interval (CI) 0.08 to 1.63) or opioid positive urine drug tests (RR 0.81, 95% CI 0.56 to 1.18). There was low quality evidence from three studies of no difference in retention between buprenorphine and methadone maintenance treatment (RR 0.69, 95% CI 0.39 to 1.22). There was moderate quality evidence from two studies of no difference between methadone and buprenorphine on adverse events (RR 1.10, 95% CI 0.64 to 1.91). We found low quality evidence from three studies favouring maintenance buprenorphine treatment over detoxification or psychological treatment in terms of fewer opioid positive urine drug tests (RR 0.63, 95% CI 0.43 to 0.91) and self reported opioid use in the past 30 days (RR 0.54, 95% CI 0.31 to 0.93). There was no difference on days of unsanctioned opioid use (standardised mean difference (SMD) -0.31, 95% CI -0.66 to 0.04). There was moderate quality evidence favouring buprenorphine maintenance over detoxification or psychological treatment on retention in treatment (RR 0.33, 95% CI 0.23 to 0.47). There was moderate quality evidence favouring buprenorphine maintenance over detoxification or psychological treatment on adverse events (RR 0.19, 95% CI 0.06 to 0.57). The main weaknesses in the quality of the data was the use of open-label study designs."	agonist pharmacotherapy for pharmaceutical opioid dependence. Methadone or buprenorphine appeared equally effective. Maintenance treatment with buprenorphine appeared more effective than detoxification or psychological treatments. Due to the overall low to moderate quality of the evidence and small sample sizes, there is the possibility that the further research may change these findings."
	"Background There are increasing concerns regarding pharmaceutical opioid harms including overdose and dependence, with an associated increase in treatment demand. People dependent on pharmaceutical opioids appear to differ in important ways from people who use heroin, yet most opioid agonist treatment research has been conducted in people who use heroin."			
Minozzi S, et al. (2013)[58] (Searched databases to September 2013)	Maintenance agonist treatments for opiate-dependent pregnant women	"To assess the effectiveness of any maintenance treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological intervention or psychosocial	"We found four trials with 271 pregnant women. Three compared methadone with buprenorphine and one methadone with oral slow-release morphine. Three out of four studies had adequate allocation concealment and were double-blind. The major flaw in the included studies was attrition bias: three out of four had a high drop-out rate (30% to 40%) and this was unbalanced between groups. Methadone versus buprenorphine: the drop-out rate from treatment was lower in the methadone group (risk ratio (RR) 0.64, 95% confidence interval (CI) 0.41 to 1.01, three studies, 223 participants). There was no statistically significant difference in the use of primary substance between methadone and buprenorphine (RR 1.81, 95% CI 0.70 to 4.69, two studies, 151 participants). For both, we judged the quality of	"We did not find sufficient significant differences between methadone and buprenorphine or slow-release morphine to allow us to conclude that one treatment is superior to another for all relevant outcomes. While methadone seems superior in terms of retaining patients in treatment, buprenorphine seems to lead to less severe neonatal abstinence syndrome. Additionally, even though a multi-centre, international trial with 175 pregnant women has recently been completed and its results

Author(s)	Title	Objectives	Main Results	Author's Conclusions
		interventions for child health status, neonatal mortality, retaining pregnant women in treatment and reducing the use of substances."	evidence as low. Birth weight was higher in the buprenorphine group in the two trials that could be pooled (mean difference (MD) -365.45 g (95% CI -673.84 to -57.07), two studies, 150 participants). The third study reported that there was no statistically significant difference. For APGAR score neither of the studies which compared methadone with buprenorphine found a significant difference. For both, we judged the quality of evidence as low. Many measures were used in the studies to assess neonatal abstinence syndrome. The number of newborns treated for neonatal abstinence syndrome, which is the most critical outcome, did not differ significantly between groups. We judged the quality of evidence as very low. Methadone versus slow-release morphine: there was no drop-out in either treatment group. Oral slow-release morphine seemed superior to methadone for abstinence from heroin use during pregnancy (RR 2.40, 95% CI 1.00 to 5.77, one study, 48 participants). We judged the quality of evidence as moderate. Only one study which compared methadone with buprenorphine reported side effects. For the mother there was no statistically significant difference; for the newborns in the buprenorphine group there were significantly fewer serious side effects. In the comparison between methadone and slow-release morphine no side effects were reported for the mother, whereas one child in the methadone group had central apnoea and one child in the morphine group had obstructive apnoea."	published and included in this review, the body of evidence is still too small to draw firm conclusions about the equivalence of the treatments compared. There is still a need for randomised controlled trials of adequate sample size comparing different maintenance treatments."
	"Background The prevalence of opiate use among pregnant women can range from 1% to 2% to as high as 21%. Heroin crosses the placenta and pregnant, opiate-dependent women experience a six-fold increase in maternal obstetric complications such as low birth weight, toxaemia, third trimester bleeding, malpresentation, puerperal morbidity, fetal distress and meconium aspiration. Neonatal complications include narcotic withdrawal, postnatal growth deficiency, microcephaly, neuro-behavioural problems, increased neonatal mortality and a 74-fold increase in sudden infant death syndrome."			
Minozzi S, et al. (2014)[59] (Searched databases to January 2014)	Maintenance treatments for opiate - dependent adolescents	"To assess the effectiveness of any maintenance treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological	"We included two trials involving 189 participants. One study, with 35 participants, compared methadone with levo-alpha-acetylmethadol (LAAM) for maintenance treatment lasting 16 weeks, after which patients were detoxified. The other study, with 154 participants, compared maintenance treatment with buprenorphine-naloxone and detoxification with buprenorphine. We did not perform meta-analysis because the two studies assessed different comparisons. In the study comparing methadone and LAAM, the authors declared that there was no difference in the use of a substance of abuse or social functioning (data not shown). The quality of the evidence was very low.	"It is difficult to draft conclusions on the basis of only two trials. One of the possible reasons for the lack of evidence could be the difficulty of conducting trials with young people for practical and ethical reasons. There is an urgent need for further randomised controlled trials comparing maintenance treatment with detoxification treatment or psychosocial treatment alone before carrying out studies that compare

Author(s)	Title	Objectives	Main Results	Author's Conclusions
		intervention or psychosocial interventions for retaining adolescents in treatment, reducing the use of substances and improving health and social status."	No side effects, such as nausea, vomiting, constipation, weakness or fatigue, were reported by study participants. In the comparison between buprenorphine maintenance and buprenorphine detoxification, maintenance treatment appeared to be more efficacious in retaining patients in treatment (drop-out risk ratio (RR) 0.37; 95% confidence interval (CI) 0.26 to 0.54), but not in reducing the number of patients with a positive urine test at the end of the study (RR 0.97; 95% CI 0.78 to 1.22). Self reported opioid use at one-year follow-up was significantly lower in the maintenance group, even though both groups reported a high level of opioid use (RR 0.73; 95% CI 0.57 to 0.95). More patients in the maintenance group were enrolled in other addiction treatment programmes at 12-month follow-up (RR 1.33; 95% CI 0.94 to 1.88). The quality of the evidence was low. No serious side effects attributable to buprenorphine-naloxone were reported by study participants and no patients were removed from the study due to side effects. The most common side effect was headache, which was reported by 16% to 21% of patients in both groups."	different pharmacological maintenance treatments. These studies should have long follow-up and measure relapse rates after the end of treatment and social functioning (integration at school or at work, family relationships)."
	"Background The scientific literature examining effective treatments for opioid-dependent adults clearly indicates that pharmacotherapy is a necessary and acceptable component. Nevertheless, no reviews have been published that systematically assess the effectiveness of pharmacological maintenance treatment in adolescents."			
Minozzi S, et al. (2010)[61] (Searched databases to June 2010)	Oral naltrexone maintenance treatment for opioid dependence	"To evaluate the effects of naltrexone maintenance treatment versus placebo or other treatments in preventing relapse in opioid addicts after detoxification."	"Thirteen studies, 1158 participants, met the criteria for inclusion in this review. Comparing naltrexone versus placebo or no pharmacological treatments, no statistically significant difference were noted for all the primary outcomes considered. The only outcome statistically significant in favour of naltrexone is re incarceration, RR 0.47 (95%CI 0.26-0.84), but results come only from two studies. Considering only studies were patients were forced to adherence a statistical significant difference in favour of naltrexone was found for retention and abstinence, RR 2.93 (95%CI 1.66-5.18). Comparing naltrexone versus psychotherapy, in the two considered outcomes, no statistically significant difference was found in the single study considered. Naltrexone was not superior to benzodiazepines and to buprenorphine for retention and abstinence and side effects. Results come from single studies."	"The findings of this review suggest that oral naltrexone did not perform better than treatment with placebo or no pharmacological agent with respect to the number of participants re-incarcerated during the study period. If oral naltrexone is compared with other pharmacological treatments such as benzodiazepine and buprenorphine, no statistically significant difference was found. The percentage of people retained in treatment in the included studies is however low (28%). The conclusion of this review is that the studies conducted have not allowed an adequate evaluation of oral naltrexone treatment in the field of opioid dependence. Consequently, maintenance therapy with naltrexone cannot yet be considered a treatment which has been scientifically

Author(s)	Title	Objectives	Main Results	Author's Conclusions
				proved to be superior to other kinds of treatment."
	"Background Research on clinical application of oral naltrexone agrees on several things. From a pharmacological perspective, naltrexone works. From an applied perspective, the medication compliance and the retention rates are poor."			
Amato , et al.(2011)[63] (Searched databases to 2003, 2008, an d2011 depending on databases searched)	Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification	"To evaluate the effectiveness of any psychosocial plus any pharmacological interventions versus any pharmacological alone for opioid detoxification, in helping patients to complete the treatment, reduce the use of substances and improve health and social status."	"Eleven studies, 1592 participants, fulfilled the criteria of inclusion and were included in the review. The studies considered five different psychosocial interventions and two pharmacological treatments (methadone and buprenorphine). Compared to any pharmacological treatment alone, the association of any psychosocial with any pharmacological was shown to significantly reduce dropouts RR 0.71 (95% CI 0.59 to 0.85), use of opiate during the treatment, RR 0.82 (95% CI 0.71 to 0.93), at follow up RR 0.66 (95% IC 0.53 to 0.82) and clinical absences during the treatment RR 0.48 (95%CI 0.38 to 0.59). Moreover, with the evidence currently available, there are no data supporting a single psychosocial approach."	"Psychosocial treatments offered in addition to pharmacological detoxification treatments are effective in terms of completion of treatment, use of opiate, participants abstinent at follow-up and clinical attendance. The evidence produced by this review is limited due to the small number of participants included in the studies, the heterogeneity of the assessment or the lack of detailed outcome information that prevented the possibility of cumulative analysis for several outcomes. Nevertheless it seems desirable to develop adjunct psychosocial approaches that might make detoxification more effective."
	"Background Different pharmacological approaches aimed at opioid detoxification are effective. Nevertheless a majority of patients relapse to heroin use, and relapses are a substantial problem in the rehabilitation of heroin users. Some studies have suggested that the sorts of symptoms which are most distressing to addicts during detoxification are psychological rather than physiological symptoms associated with the withdrawal syndrome."			
Ferri M, et al. (2013)[62] (Searched databases to April 2013)	Slow-release oral morphine as maintenance therapy for opioid dependence	"To evaluate the efficacy of SROM as an alternative maintenance pharmacotherapy for the treatment of opioid dependence."	"Three studies with 195 participants were included in the review. Two were cross-over trials and one was a parallel group RCT. The retention in treatment appeared superior to 80% in all the three studies (without significant difference with controls). Nevertheless, it has to be underlined that the studies had different durations. One lasted six months, and the other two lasted six and seven weeks. The use of opioids during SROM provision varied from lower to non-statistically or clinically different from comparison interventions, whereas there were no differences as far as the use of other substances was concerned. SROM seemed to be equal to comparison interventions for severity of dependence, or mental health/social functioning, but there was a trend for less severe opiate withdrawal symptoms in comparison with methadone (withdrawal score 2.2 vs. 4.8, P value = 0.06). Morphine was	"The present review did not identify sufficient evidence to assess the effectiveness of SROM for opioid maintenance because only three studies meeting our inclusion criteria have been identified. Two studies suggested a possible reduction of opioid use in people taking SROM. In another study, the use of SROM was associated with fewer depressive symptoms. Retention in treatment was not significantly different among compared interventions while the adverse effects were

Author(s)	Title	Objectives	Main Results	Author's Conclusions
			generally well tolerated and was preferred by a proportion of participants (seven of nine people in one study). Morphine appeared to reduce cravings, depressive symptoms (measured using the Beck Depression Inventory; P value < 0.001), physical complaints (measured using the Beschwerde-Liste (BL); P value < 0.001) and anxiety symptoms (P value = 0.008). Quality of life in people treated with SROM resulted in no significant difference or a worst outcome than in those taking methadone and buprenorphine. Other social functioning measures, such as finances, family and overall satisfaction, scored better in people maintained with the comparison substances than in those maintained with SROM. In particular, people taking methadone showed more favourable values for leisure time (5.4 vs. 3.7, P value < 0.001), housing (6.1 vs. 4.7, P value < 0.023), partnerships (5.7 vs. 4.2, P value = 0.034), friend and acquaintances (5.6 vs. 4.4, P value = 0.003), mental health (5.0 vs. 3.4, P value = 0.002) and self esteem (8.2 vs. 5.7, P value = 0.002) compared to people taking SROM; while people taking buprenorphine obtained better scores for physical health. Medical adverse events were consistently higher in people in SROM than in the comparison groups. None of the studies included people with a documented poor response"	more frequent with the people given SROM."
	"Background Opioid substitution treatments are effective in retaining people in treatment and suppressing heroin use. An open question remains whether slow-release oral morphine (SROM) could represent a possible alternative for opioid-dependent people who respond poorly to other available maintenance treatments."			
Pani PP, et al. (2010)[64]	Pharmacological treatment for depression during opioid agonist treatment for opioid dependence	"To evaluate the efficacy and the acceptability of antidepressants for the treatment of depressed opioid dependents treated with opioid agonists."	"Seven studies, 482 participants, met the inclusion criteria. - Comparing antidepressant with placebo, no statistically significant results for dropouts. Selecting studies with low risk of bias, 325 participants, results favour placebo, RR 1.40 (CI 95% 1.00 to 1.96). For severity of depression, results from two studies, 183 participants, favour antidepressants utilising Clinical Global Impression Scale RR 1.92 (CI 95% 1.26 to 2.94), while another study, 95 participants, utilising the Hamilton Depression Rating Scale, did not find a statistically significant difference RR 0.96 (CI 95% 0.54 to 1.71). For adverse events, result favour placebo, four studies, 311 participants, RR 2.90 (Cl 95% 1.23 to 6.86). For drug use, three studies, 211 participants, it was not possible to pool data because outcomes' measures were not comparable. Looking at singular studies, no statistically significant difference was seen. - Comparing different classes of antidepressants, the results favour tricyclics for severity of depression, two studies, 183 participants, RR	"There is low evidence, at the present, supporting the clinical use of antidepressants for the treatment of depressed opioid addicts in treatment with opioid agonists. There is a need of larger randomised studies investigating relevant outcomes, safety issues and reporting data to allow comparison of results."

Author(s)	Title	Objectives	Main Results	Author's Conclusions
			1.92 (Cl 95% 1.26 to 2.94) and favour placebo for adverse events, two studies, 172 participants, RR 3.11 (Cl 95% 1.06 to 9.12)."	
	"Background Lifetime prevalence of depression in subjects with opioid dependence is higher than in the general population (44-54% versus 16%) and represents a risk factor for morbidity and mortality. For patients on opioid agonist treatment, current prevalence rates of depression ranges between 10 and 30%, influencing negatively the outcome of the treatment."			
Gowing L, et al. (2011)[60] (Searched databases to May 2011)	Oral substitution treatment of injecting opioid users for prevention of HIV infection	"To assess the effect of oral substitution treatment for opioid dependent injecting drug users on risk behaviours and rates of HIV infections"	"Thirty-eight studies, involving some 12,400 participants, were included. The majority were descriptive studies, or randomisation processes did not relate to the data extracted, and most studies were judged to be at high risk of bias. Studies consistently show that oral substitution treatment for opioid-dependent injecting drug users with methadone or buprenorphine is associated with statistically significant reductions in illicit opioid use, injecting use and sharing of injecting equipment. It is also associated with reductions in the proportion of injecting drug users reporting multiple sex partners or exchanges of sex for drugs or money, but has little effect on condom use. It appears that the reductions in risk behaviours related to drug use do translate into reductions in cases of HIV infection. However, because of the high risk of bias and variability in several aspects of the studies, combined totals were not calculated."	"Oral substitution treatment for injecting opioid users reduces drug-related behaviours with a high risk of HIV transmission, but has less effect on sex-related risk behaviours. The lack of data from randomised controlled studies limits the strength of the evidence presented in this review."
	"Background Injecting drug users are vulnerable to infection with Human Immunodeficiency Virus (HIV) and other blood borne viruses as a result of collective use of injecting equipment as well as sexual behaviour."			
Amato L, et al. (2013)[65] Searched databases to 2004, 2007, and 2012 depending on databases searched)	Methadone at tapered doses for the management of opioid withdrawal	"To evaluate the effectiveness of tapered methadone compared with other detoxification treatments and placebo in managing opioid withdrawal on completion of detoxification and relapse rate."	"Twenty-three trials involving 2467 people were included. Comparing methadone versus any other pharmacological treatment, we observed no clinical difference between the two treatments in terms of completion of treatment, 16 studies 1381 participants, risk ratio (RR) 1.08 (95% confidence interval (CI) 0.97 to 1.21); number of participants abstinent at follow-up, three studies, 386 participants RR 0.98 (95% CI 0.70 to 1.37); degree of discomfort for withdrawal symptoms and adverse events, although it was impossible to pool data for the last two outcomes. These results were confirmed also when we considered the single comparisons: methadone with: adrenergic agonists (11 studies), other opioid agonists (eight studies), anxiolytic (two studies), paiduyangsheng (one study). Comparing methadone with placebo (two studies) more severe withdrawal and more drop-outs were found in the placebo group.	"Data from literature are hardly comparable; programs vary widely with regard to the assessment of outcome measures, impairing the application of meta-analysis. The studies included in this review confirm that slow tapering with temporary substitution of long- acting opioids, can reduce withdrawal severity. Nevertheless, the majority of patients relapsed to heroin use."

Author(s)	Title	Objectives	Main Results	Author's Conclusions
			The results indicate that the medications used in the included studies are similar in terms of overall effectiveness, although symptoms experienced by participants differed according to the medication used and the program adopted."	
	"Background The evidence of tapered methadone's efficacy in managing opioid withdrawal has been systematically evaluated in the previous version of this review that needs to be updated."			

Other Reviews in Cochrane Library: The Centre for Reviews and Dissemination (DARE; University of York) has determined that it meets the DARE scientific quality criteria for a systematic review[139]

Author(s)	Title	Objectives	Main Results	Author's Conclusions
Brogly SB, et al. (2014)[66]	Prenatal buprenorphine versus methadone exposure and neonatal outcomes: systematic review and meta-analysis.	"Increasing rates of maternal opioid use during pregnancy and neonatal withdrawal, termed neonatal abstinence syndrome (NAS), are public health concerns. Prenatal buprenorphine maintenance treatment (BMT) versus methadone maintenance treatment (MMT) may improve neonatal outcomes, but associations vary. To summarize evidence, we used a random-effects meta-analysis model and estimated summary measures of BMT versus MMT on several outcomes.	"Subjects were 515 neonates whose mothers received BMT and 855 neonates whose mothers received MMT and who were born from 1996 to 2012 and who were included in 12 studies. The unadjusted NAS treatment risk was lower (risk ratio=0.90, 95% confidence interval (CI): 0.81, 0.98) and mean length of hospital stay shorter (-7.23 days, 95% CI: -10.64, -3.83) in BMT-exposed versus MMT-exposed neonates. In treated neonates, NAS treatment duration was shorter (-8.46 days, 95% CI: -14.48, -2.44) and morphine dose lower (-3.60 mg, 95% CI: -7.26, 0.07) in those exposed to BMT. BMT-exposed neonates had higher mean gestational age and greater weight, length, and head circumference at birth. Fewer women treated with BMT used illicit opioids near delivery (risk ratio=0.44, 95% CI: 0.28, 0.70). Simulations suggested that confounding by indication could account for some of the observed differences."	"Prenatal BMT versus MMT may improve neonatal outcomes, but bias may contribute to this protective association. Further evidence is needed to guide treatment choices."

Author(s)	Title	Objectives	Main Results	Author's Conclusions
		Sensitivity analyses evaluated confounding, publication bias, and heterogeneity."		
Yee A, et al. (2014)[67]	The prevalence of sexual dysfunction among male patients on methadone and buprenorphine treatments: a meta-analysis study.	"We conducted a meta-analysis to evaluate the prevalence of sexual dysfunction among male patients on methadone and buprenorphine treatments."	"A total of 1,570 participants from 16 eligible studies were identified in this meta-analysis. The studies provided prevalence estimates for sexual dysfunction among methadone users with a meta-analytical pooled prevalence of 52% (95% confidence interval [CI], 0.39-0.65). Only four studies compared sexual dysfunction between the two groups, with a significantly higher combined odds ratio in the methadone group (OR = 4.01, 95% CI, 1.52-10.55, P = 0.0049)."	"Evidence showed that the prevalence of sexual dysfunction was higher among the users of methadone compared with buprenorphine. Patients with sexual difficulty while on methadone treatment were advised to switch to buprenorphine."
	"INTRODUCTION: For many years, methadone has been recognized as an effective maintenance treatment for opioid dependence. However, of the many adverse events reported, sexual dysfunction is one of the most common side effects. **METHODS:** Relevant studies published from inception until December 2012 were identified by searching PubMed, OVID, and Embase. Studies were selected using prior defined criteria. Heterogeneity, publication bias, and odds ratio were assessed thoroughly. **MAIN OUTCOME MEASURES:** To examine the prevalence and odds ratio of sexual dysfunctions among the methadone and buprenorphine groups."			
Hedrich D, et al. (2012)[68,69] *Databases searched to 2010*	The effectiveness of opioid maintenance treatment in prison settings: a systematic review	To review the effectiveness of opioid management treatment in prison and after prison release.	"Twenty-one studies were included: six randomised trials (1,023 participants) and 15 observational studies (approximately 7,438 participants). Six studies were judged to be good quality, nine were acceptable quality and six were of inadequate quality. Four of the six randomised trials were judged to have adequate randomisation, two had adequate allocation concealment, four had comparable groups at baseline, three adequately addressed incomplete outcome data and two used intention-to-treat analysis. Follow-up ranged from 12 days to four years.Outcomes during imprisonment: Six studies (two trials and four observational studies) reported significant reductions in illicit drug use (mostly heroin) with maintenance treatment based on biological markers. Five studies (two trials and three observational studies) reported significant reductions in heroin injecting in prison and five studies also reported reductions in needle sharing. One trial reported HIV/hepatitis C seroconversion in prison, HIV prevalence at baseline was zero and there were no seroconversions. Baseline hepatitis C	**"CRD summary:** This review concluded that the benefits of prison opioid maintenance treatment were similar to those in community settings. Although the conduct of the review was generally good the conclusion does not reflect the main results due to a lack of comparison between prison and community interventions." **"Authors' conclusions:** The benefits of prison opioid maintenance treatment were similar to those in community settings. For people receiving maintenance treatment before imprisonment, prison treatment provided treatment continuity."

Author(s)	Title	Objectives	Main Results	Author's Conclusions
			prevalence was 76% in the treatment group and 72% in controls and four people in each group seroconverted. One observational study reported that serious drug violations reduced among offenders in the maintenance treatment group and increased in the untreated group.Post-release outcomes: Four studies (three trials and one observational study) compared pre-release opioid maintenance treatment to no treatment and reported significantly higher levels of post-release treatment entry and retention for the treatment group. One trial that compared buprenorphine to low-dose methadone found that those on buprenorphine were more likely to intend to continue treatment after release and report to their assigned centre. Another study reported similar treatment retention rates at six months. Four out of five studies (three trials and one observational) that reported on opioid use after prison release showed significant reductions in heroin use for maintenance treatment. One of the four studies that reported on self-reported criminal activity found significantly less criminal activity among those who had received pre-release treatment but this did not remain after six months. Nine studies compared maintenance treatment to no treatment and reported on re-incarceration. Four (two trials and two observational studies) reported significantly lower rates of re-incarceration amongst the treated subjects although in one trial this difference was only seen up to three months after release. Two studies compared different treatment doses, one found higher reductions in re-incarceration with high-dose methadone (>60mg) than low-dose methadone (<30mg); the other trial reported no significant differences. Three studies reported on mortality and in one trial no significant differences were seen over a four-year period. Two other studies reported all-cause mortality rates between eight and 14 per 1,000 person-years for treatment. Four observational studies reported results for the continuity or disruption of maintenance treatment between prison and community. Full details were reported in the paper."	
	"CRD commentary: This review had clear and reproducible inclusion criteria. The search strategy covered a range of databases and other sources without language restrictions so potential bias was reduced. Study selection and data extraction were performed in duplicate; it was unclear whether this also applied to quality assessment. The quality of the evidence was assessed using different tools depending on study design. The possible impact of bias on study results was reported. The results were reported narratively due to methodological variation between the studies. Overall the review conduct was generally good with a broad literature search and methods used to reduce bias. However the conclusion does not reflect the main results due to a lack of comparison between prison and community interventions."			
Larney S. (2010)[70,140]	Does opioid substitution treatment in	"To evaluate the effectiveness of prison-based opioid	"Five studies were included in the review (n=1.036 participants, range 43 to 518): one randomised controlled trial (n=253 participants), one quasi-randomised study (n=69 participants), and three non-randomised	**"CRD summary:** This review found that opioid substitution treatment may help reduce human immunodeficiency virus (HIV)

Author(s)	Title	Objectives	Main Results	Author's Conclusions
	prisons reduce injecting-related HIV risk behaviours? A systematic review.	substitution treatment for reducing injecting-related human immunodeficiency virus (HIV) risk behaviours."	studies (n=714 participants). Groups were comparable at baseline in three studies. Follow-up rates ranged from 52 to 68% in the two studies with follow-up; neither used intention-to-treat analysis. The three other studies were cross-sectional and did not report participation rates; the representativeness of their samples was uncertain.Illicit opioid use was significantly reduced in the treatment group compared to controls in all four studies reporting this outcome, with risk reductions ranging from 62 to 91%. In the fifth study, there was a statistically significant reduction over time in the number of institutional drug charges among treated participants compared with control groups.Two of three relevant studies reported a significant reduction (55% and 75%) in injecting drug use in the opioid substitution treatment group compared with the control group; the third study reported no statistically significant difference between the groups.Three studies reported a statistically significant reduction in needle and syringe sharing in the treatment group compared to controls, with risk reductions ranging from 47 to 73%. None of the studies reported HIV incidence. The review reported risk ratios and 95% confidence intervals for all pre-specified outcomes for each study."	risk behaviours in prison, but that further research is needed. The review was well conducted in most respects and the author's cautious conclusions appear reliable." **"Authors' conclusions:** Opioid substitution treatment may help to reduce HIV risk behaviours in prison, but further research is needed."
	Note: Included studies were set in Iran, Australia, Puerto Rico and Australia. **"CRD commentary:** The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies in any language. However, specific attempts did not seem to have been made to retrieve unpublished studies. Search dates were not reported. The review had a single author, and it appeared that study selection and validity assessment, as well as data extraction, were undertaken by this lone author; lack of an independent check of review processes meant that the review was at increased risk of reviewer bias and error.The decision to combine the studies by narrative synthesis was appropriate, given their heterogeneity. The author noted a number of limitations in the evidence, including the small amount of data available, low rates of follow-up, lack of intentional-to-treat analysis, potentially unrepresentative samples and ethical concerns. Study quality was also taken into account in the interpretation of findings. The author advised that the results should be viewed with caution.The review was well conducted in most respects and the author's cautious conclusions appear reliable. **Implications of the review for practice and research:** Practice: The author stated that opioid substitution treatment should be implemented in prisons as part of comprehensive HIV prevention programme, which should also include provision of condoms, and sterile injecting and tattooing equipment.Research: The author stated that methodologically robust studies are required to guide further development and implementation of prison-based opioid substitution treatment."			

Appendix 5 – Additional Data

*Some maximum average daily doses (ADDs) appear to be outliers and are likely based on some incorrect data (e.g. number of days' supply may be incorrect)

Generic	Description	MAX ADD	Dose	Qty	Days
Buprenorphine HCl	Buprenorphine Sublingual Tablet	232*	8	29	1
Buprenorphine HCl	Buprenorphine Sublingual Tablet	85.3*	8	64	6
Buprenorphine HCl	Buprenorphine Sublingual Tablet	40	8	75	15
Buprenorphine HCl	Buprenorphine Sublingual Tablet	34.3	8	30	7
Buprenorphine HCl	Buprenorphine Sublingual Tablet	32.7	8	45	11
Buprenorphine HCl	Buprenorphine Sublingual Tablet	32.7	8	90	22
Buprenorphine HCl	Buprenorphine Sublingual Tablet	32	8	48	12
Buprenorphine HCl	Buprenorphine Sublingual Tablet	32	8	120	30
Buprenorphine HCl	Buprenorphine Sublingual Tablet	32	8	4	1
Buprenorphine HCl	Buprenorphine Sublingual Tablet	32	8	56	14

Generic	Description	MAX ADD	Dose	Qty	Days
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	180*	8	90	4
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	112*	8	14	1
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	96	8	60	5
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	84	8	21	2
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	80	8	20	2
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	72	8	45	5
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	72	8	90	10
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	64	8	8	1
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	64	8	16	2
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	60	2	90	3
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	60	8	30	4
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	56	8	14	2
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	56	8	14	2
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	56	8	21	3
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	51.4	8	45	7
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	50.7	8	19	3
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	48. 6	8	85	14
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	48	8	18	3
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	48	8	42	7
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	48	8	90	15
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	48	12	60	15
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	44	8	22	4
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	44	8	11	2
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	42.7	8	16	3
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	42.3	8	37	7

Generic	Description	MAX ADD	Dose	Qty	Days
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	41.3	12	31	9
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	40.8	4	102	10
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	40	8	70	14
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	40	8	75	15
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	40	8	5	1
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	40	8	10	2
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	40	8	5	1
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	40	8	10	2
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	40	8	75	15
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	40	8	75	15
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	40	8	25	5
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	40	8	5	1
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	40	8	5	1
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	39.1	8	83	17
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	36.6	8	64	14
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	36.3	8	68	15
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	36.3	8	68	15
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	36	8	45	10
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	36	8	45	10
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	36	8	27	6
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	36	8	9	2
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	36	8	9	2
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	36	8	9	2
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	36	8	18	4
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	36	8	18	4
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	35.2	8	22	5
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	34.3	8	30	7
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	34.3	8	30	7
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	34.3	8	30	7
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	34.3	8	30	7
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	34.3	8	30	7
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	34.3	8	30	7
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	34.3	8	30	7
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	34.3	8	30	7
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	34.3	8	30	7
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	34.3	8	30	7
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	34.3	8	30	7
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	33.3	8	25	6
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	33.3	8	50	12
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	32.7	8	90	22
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	32.7	8	90	22
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	32.7	8	90	22
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	32.7	8	90	22

Generic	Description	MAX ADD	Dose	Qty	Days
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	32.7	8	90	22
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Film	32.7	8	45	11

Generic	Description	MAX ADD	Dose	Qty	Days
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Tablet	144*	8	54	3
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Tablet	120*	8	30	2
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Tablet	64*	8	40	5
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Tablet	53.3	8	20	3
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Tablet	50.7	8	76	12
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Tablet	40	8	5	1
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Tablet	40	8	120	24
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Tablet	40	8	65	13
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Tablet	34.3	8	30	7
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Tablet	34.3	8	30	7
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Tablet	34.3	8	30	7
Buprenorphine HCl-Naloxone HCl Dihydrate	Suboxone Sublingual Tablet	34	2	17	1

Generic	Description	ADD	Dose	Qty	Days
Buprenorphine HCl-Naloxone HCl Dihydrate	Buprenorphine-Naloxone Sublingual Tablet	60	8	45	6
Buprenorphine HCl-Naloxone HCl Dihydrate	Buprenorphine-Naloxone Sublingual Tablet	32	8	120	30

Generic	Description	ADD	Dose	Qty	Days
Buprenorphine HCl-Naloxone HCl Dihydrate	Zubsolv Sublingual Tablet	37.1	5.7	26	4
Buprenorphine HCl-Naloxone HCl Dihydrate	Zubsolv Sublingual Tablet	24.4	5.7	30	7
Buprenorphine HCl-Naloxone HCl Dihydrate	Zubsolv Sublingual Tablet	24.4	5.7	30	7
Buprenorphine HCl-Naloxone HCl Dihydrate	Zubsolv Sublingual Tablet	23.3	5.7	90	22
Buprenorphine HCl-Naloxone HCl Dihydrate	Zubsolv Sublingual Tablet	23.3	5.7	90	22
Buprenorphine HCl-Naloxone HCl Dihydrate	Zubsolv Sublingual Tablet	22.8	5.7	8	2
Buprenorphine HCl-Naloxone HCl Dihydrate	Zubsolv Sublingual Tablet	20	5.7	35	10
Buprenorphine HCl-Naloxone HCl Dihydrate	Zubsolv Sublingual Tablet	18.6	5.7	49	15
Buprenorphine HCl-Naloxone HCl Dihydrate	Zubsolv Sublingual Tablet	17.8	5.7	25	8
Buprenorphine HCl-Naloxone HCl Dihydrate	Zubsolv Sublingual Tablet	17.5	5.7	80	26

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